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MEDICAL AND PHARMACEUTICAL TARGETS IN NORTHERN GERMANY AND HOLLAND



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MEDICAL AND PHARMACEUTICAL TARGETS
IN NORTHERN GERMANY AND HOLLAND

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MEDICAL

COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE
G-2 Division SHAFF (Rear) APO 413.

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Personnel of Team.

All of the team with the exception of Dr. Rice and Dr. Hall are members of CIOS Team 425. This report also contains considerable information acquired by Dr. Rice and Dr. Hall during the course of their activities as CAFT Assessors.

I. INTRODUCTION

From 14 June to 5 July, 1945, C.I.C.S. Team 425 visited and investigated a number of medical and pharmaceutical targets in northern Germany and Holland. In order to present the information obtained as clearly as possible, this report has been divided into two major sections. The first section deals with items of medical interest, and is based upon visits to the following targets.

- a) Flakturm Krankenhaus, Hamburg
- b) Eppendorf Hospital, Medical Faculty, University of Hamburg
- c) Institute für Schiffs- und Tropenkrankheit, Hamburg
- d) Professor Dr. Horst Habs, former Director of the Institute of Hygiene, Hamburg
- e) Rijks Institut voor de Volksgezondheid (State Institute of Public Health), Utrecht
- f) Laboratory of Organic Chemistry, University of Utrecht
- g) Botanical Laboratory, Utrecht
- h) Laboratory of Physiological Chemistry, Netherlands Institute of Nutrition, Amsterdam
- i) Medical Faculty, University of Utrecht
- j) Institute of Tropical Medicine, Leiden
- k) Medical Faculty, University of Leiden
- l) Institute of Tropical Medicine, Amsterdam
- m) Medical Faculty, University of Amsterdam
- n) Tierärztliche Hochschule, Hannover.

The next section is concerned with pharmaceutical information and is based on investigation of the following targets:

- a) P. Beiersdorff & Co., Hamburg
- b) Chemische Fabrik Promonta, Hamburg
- c) Riedel-de Haen A.G., Hamburg
- d) C. H. Boehringer Sohn, Hamburg
- e) Nordmark Werke, Hamburg
- f) Dr. Chr. Brunnegräber Chemische Fabrik & Co., Lubeck
- g) Benger & Co., Hannover

- h) Riedel-de Haen A.G. Werke, Seelze near Hannover
- i) Chininfabrik Braunschweig Fuchler & Co.,
Braunschweig
- j) Orbis-Werke, Braunschweig.
- k) Dr. Hans Brückner & Co., Schmolke,
Bortfeld near Braunschweig
- l) Organon N.V., Oss, Holland
- m) I.G. Farbenindustrie A.G., Institut zur Bekämpfung
der Virusschweinepest (Behring Institut),
Fystrup a.d.W. i
- n) Hamburger Serum Werke G.m.b.H., Hamburg
- o) Schilke & Mayer A.G., Hamburg

A number of targets originally scheduled for investigation were not visited. These are listed below together with the reasons for not visiting them.

- a) Athenstaedt & Redeker Chemische Fabrik, Bremen - destroyed
- b) Medical Faculty, University of Kiel - Informed on 16 June 1945 by CAFT Assessors, J.B. Rice and S.A. Hall that this target was largely destroyed and that no investigation was required.
- c) C.F. Asche & Co., Hamburg - destroyed
- d) Bakt Laboratorium, Hannover - destroyed
- e) Huper & Schmidt, Hannover - destroyed
- f) Pharmakognostisches Institut der Technischen Hochschule, Braunschweig - abandoned on the basis of CAFT assessment report

Finally, it should be noted that several items in this report (Kuntscher pin, Degkwitz's aimed injections, the Institut für Schiffs- und Tropenkrankheiten, Professor Habs, and the Tierärztliche Hochschule, Hannover) are based in considerable part on information supplied by CAFT assessors Dr. J.B. Rice and Dr. S.A. Hall.

II. MEDICAL TARGETS IN NORTHERN GERMANY AND HOLLAND

1. Internal Splinting of Fractures (Küntscher Marknagelung).

The Küntscher method for the internal splinting of fractures of the long bone was first described by Professor Küntscher of Kiel in 1941. His original papers appeared in the Zentralblatt für Chirurgie and in Der Chirurg. The most recent description of the method, as well as an evaluation of the results in about 1,000 cases, are to be found in Lorenz Böhler: Die Technik der Knochenbruchbehandlung im Frieden und im Kriege. Band III. Die Marknagelung nach Küntscher, Wien, 1944.

Information on this subject was obtained from Dr. Adam, of the Flakturm Krankenhaus in Hamburg. Dr. Adam stated that he had used the Küntscher technique with success in about 200 cases, but other German surgeons have had wider experience. Every surgical clinic in Germany is familiar with the Küntscher method, and it enjoys widespread use in both civilian and military practice. The method consists in aligning the fragments, and then inserting a long steel rod (made of a special steel, V2A Krupp) into practically the entire length of the medullary cavity of both fragments which are thus held in position by being threaded on the rod. The introduction is effected through a small skin incision, and the rod is left inside the bone until union is complete. In the case of fractured femora this period may be as long as a year. The patients use their limbs immediately. Patients with a fractured femur or tibia may even walk the day after the operation without other splintage. Dr. Adam stated that the operation of insertion takes only a few minutes. Complications have been infrequent.

Further information was obtained by interrogation of Dr. Schröder, also of the Flakturm Krankenhaus, and Dr. P. Sunder Plassmann of the Surgical Clinic, University of Kiel. These physicians corroborated the statements of Dr. Adam and added the following: The Küntscher method is suitable for use in all fractures of the long bones, both simple and compound, regardless of the degree of comminution. The only contraindication is severe infection. When moderate infection is present, the method is used in conjunction with topical application of sulfonamide powder, and oral and parenteral administration of sulfonamides.

It is worth noting that the Küntscher method has even been used in veterinary practice. According to information obtained

from the Director of the Staatliches Veterinär- Untersuchungsamt, Hammer Strasse 147, Münster, it has been found practicable in fractures of the long bones in smaller animals (dogs, cats, etc.), but unsuitable for larger animals such as horses and cattle.

In general, the following advantages are claimed for the Kuntscher method:-

- a) It is possible to obtain perfect alignment in practically all cases.
- b) Bones heal faster because immobilization is more complete, and callus formation is stimulated by the rod.
- c) After fracture of the femur, children may be permitted to walk in about ten days, while adults may require a few more days.
- d) There is no danger of ankylosis in elderly patients, because normal movements may be instituted from the beginning.
- e) Because of early exercise there is no danger of muscular atrophy.

It is claimed that compound fractures with a moderate degree of infection are no more difficult to handle than when older methods are used. In the experience of the physicians who were interrogated, the use of the splint has not been the cause of infection in any instance. The occurrence of fat embolism has been reported, although the experience of the men cited above did not include such cases. It is said to complicate less than 1 % of cases. There is no effect on the blood picture because of bone-marrow destruction, even when as many as five bones have been splinted at the same time. The bone-marrow is said to regenerate promptly when the splint is removed. It is considered the method of choice for fractures of the humerus, radius, ulna, femur, tibia and fibula. No other method of immobilization, i.e., plaster or bandages, is used with the splints. It is claimed that the splint causes no foreign body reaction, and has been left in situ for as long as one year, although it is usually removed much earlier depending upon roentgenological evidence of healing.

2. Eppendorf Hospital, Medical Faculty, University of Hamburg.

Although a number of the hospital units were either completely destroyed or severely damaged, the physiological, biochemical and pharmacological laboratories were found to be intact and well-equipped.

Interviews were held with members of the staff; and the information which was obtained and is believed to be of significance is reported in the following sections.

A. The Technique of Aimed Injections.

Dr. Rudolf Degkwitz is chief of the Department of Pediatrics at the Eppendorf Hospital in Hamburg, and Dean of the Medical Faculty of the University of Hamburg. He is highly regarded by his associates at the University, and is considered an outstanding scientist. Dr. Degkwitz gives the impression of being a sound and able investigator who is not likely to entertain "half-baked" ideas. Associated with him in the chemical part of his research work has been Dr. Cadenbach of the Department of Chemistry of the University.

Dr. Degkwitz's principal research during the last nine years (two of which he spent in a concentration camp) has been directed to developing his idea of "aimed injections". The method comprises intravenous injection of water-insoluble substances of varying shape and size in aqueous suspension, it being claimed that depending on the shape and size of a particular particle it can be made to lodge in a chosen site. For example, the lungs, liver, spleen or bone marrow can selectively absorb a substance under examination.

The theory behind the technique is that therapeutic agents can be concentrated in the lung, liver, spleen and bone marrow by physical means, and can thus be made to exercise their maximum effect on these organs with a minimum amount of toxicity for other organs.

According to Dr. Degkwitz, the diameter of the capillaries of these organs varies in size from largest to smallest in this order: lung, liver, spleen, bone marrow. If particles of

relatively large size are injected intravenously, they will be filtered out by the lung capillaries and thus be concentrated in the lung. Particles of smaller size will pass through the lung capillaries and be removed and concentrated in the liver; still smaller particles will pass through both lung and liver and be retained by the spleen. The smallest particles with which he works will pass through all these organs and be concentrated in the bone marrow. According to Dr. Degkwitz, two other considerations influence this process, i.e., the shape of the particle and the presence of endothelial cells in the liver, spleen, and bone marrow. He thinks that in the case of the lung the mechanism of filtration is purely mechanical. Spherical particles pass through any capillary bed more readily than do needles because the latter tend to catch in the convolutions of the capillaries. The particles with which Dr. Degkwitz works vary in size from 0.00002 mm to 0.00005 mm.

The problem as Dr. Degkwitz saw it was to obtain particles of the proper size that would have a therapeutic effect. The clue to the solution of part of the problem was found in intercellular fibers. These fibers are crystalline in structure, but under ordinary circumstances crystals form only from pure solutions. However, the protoplasm from which these crystals are formed are not pure solutions but contain many dissolved substances. He reasoned, therefore, that protoplasm must contain substances favoring crystallization. Upon investigation, he found that protoplasm did in fact contain substances which promote crystallization, and these are lipoids, soaps, lecithin, and phosphatids. Albumin, glycogen and certain colloidal substances prevent or hinder crystallization. Dr. Degkwitz theorized that the size of crystals could be controlled by altering the balance in the solution between substances that promote and those that hinder crystallization.

A series of experiments was undertaken by Dr. Degkwitz and Cadenbach, which eventually resulted in their being able to make particles of any desired size of substances which are soluble in organic solvents such as alcohol or acetone but insoluble in water. They have worked with many such substances, including cholesterol, Sudan red, and sulfanilamide and its derivatives.

Their technique briefly is as follows: They dissolve the substance in the organic solvent and pour it into water. Crystallization starts at once and crystal size can be controlled with certainty by adding an inhibitive agent, such as albumen, at the

right moment. Other factors such as temperature, purity of the solution, and concentration of the substance in the organic solvent, influence the speed of the reaction.

Dr. Cadenbach says that in the course of crystallization the first particles formed are always spherical, and as the particles increase in size, characteristic crystals in the shape of needles or plates are formed. He says that the spheres are isotropic and the largest needles are anisotropic. The spheres, according to Dr. Cadenbach, may not be considered true crystals but as conglomerates of particles or molecules.

In the laboratory, Dr. Cadenbach demonstrated the preparation of spheres and crystals of different sizes from cholesterol.

Dr. Degkwitz showed a motion picture on the effects of 0.001% suspensions of cholesterol of different particle size on paramoecium caudatum. The motion picture (in color) also showed animals injected intravenously with suspensions of large particles of Sudan blue. The lungs of these animals were quite blue, whereas the liver and other organs were of natural color. Other animals injected with the same substance but of smaller particle size showed normally colored lungs but blue liver. The motion picture also showed cultures of Paramecium to which cholesterol particles of different sizes were added. In the culture to which large particles had been added, the Paramecia were unaffected, whereas in the culture to which cholesterol particles of smaller size were added, the Paramecia rapidly became motionless and died. This demonstrated the great uniformity of the particle size. The large particles were just too large to be ingested by the Paramecia and consequently they remained unaffected. The smaller particles were ingested, however, and killed the protozoa.

Dr. Degkwitz has worked with sulfonamide compounds to some extent, but the work was interrupted by his confinement in a concentration camp for anti-Nazi activities.

He had also worked with Sudan red in the treatment of tuberculosis. Sudan red was selected because of its affinity for the waxy capsule of the tubercle bacillus. Dr. Degkwitz states that Sudan red kills tubercle bacilli in culture in a concentration of from 1 to 20,000 to 1 to 40,000, a concentration which he says is non-toxic. In animal studies both bovine and human strains were

used in guinea pigs and rabbits. The bovine strain is less satisfactory because the course of the disease is too acute. About 100 to 150 animals were used in these experiments. The guinea pigs were inoculated with from ten thousand to twenty thousand human tubercle bacilli. After about two weeks 1 mg. of Sudan red per animal was injected intraperitoneally twice weekly. Treatment was continued for four to eight weeks. Untreated controls all died within eight to ten weeks. About 70% of the treated animals survived. At autopsy, treated animals show no evidence of tuberculosis.

During the two years Dr. Degkwitz spent in the concentration camp, he tried Sudan red on thirty or forty per cent of his starving companions -- about 25% of whom had tuberculosis. No results were obtained, but none were really expected because all of his patients were actually starving, and no treatment could have been expected to have been successful under these conditions.

To date the only clinical application has been the preparation of a contrast medium manufactured by Schering A.G., for use in diagnostic work on the liver and spleen. The Schering product is a suspension of a tri-hydriodide of Ethyl linolenate ($\text{CH}_3 \dots \text{CH}_2-\text{CHI}-\text{CH}_2-\text{CHI}-\text{CH}_2\text{CHI} \dots \text{COOC}_2\text{H}_5$) and is named "Hepatoselectan" when used for liver and spleen work, but the same product under the name of "Vasoselectan" is supplied as a contrast medium for arteriography. The preparations for injection are said to be stable for a period of two years. Aimed injections of Hepatoselectan have been used by Dr. Degkwitz as a procedure for the early diagnosis of cancer of the liver and spleen.

Dr. Degkwitz's early researches in this field have been reported:- DEGKWITZ: FORTSCHRITTE AUF DEM GEBIETE DER RONTGEN-STRÄHLEN. 58, 472, 1938; also KOLLOID ZEITSCHRIFT, vol. 87, No.3 (1937).

Pursuing this scheme of research, some 180 substances having long fatty side chains and thought to be capable of penetrating the fat-containing envelope of the tubercle bacillus were tried in vitro. The three most active substances, so particulated as to be absorbed in the lung were (a) p-sulphonamidophenyl-azo-d-naphthylamine, (b) the cetyl derivative of Prontalbin and, (c) the oleyl ester of p-nitrophenylsulphonemido acetic acid, of which the last named was the most active.

D. Interview of Professor Dr. E. Keeser, Professor of Pharmacology, Medical Faculty, University of Hamburg.

Professor Dr. E. Keeser was interviewed on 17 June 1945. He stated that the lack of animals, chemicals and illuminating gas were seriously handicapping the resumption of research. During the war he studied the experimental and clinical pharmacology of dinitroglycol, a new explosive. In contrast to nitroglycerine, dinitroglycol does not reduce blood pressure. Exposure of the workmen to the new explosive resulted in a number of fatalities. According to Dr. Keeser, death was caused by the poisoning of a respiratory enzyme system. In the dog, 500 mg. doses of ascorbic acid administered subcutaneously or per os counteracted this toxic effect. In man, a prophylactic dose of 100 mg. daily per os appeared to be effective. Ascorbic acid is not, however, an effective antidote against nitroglycerine poisoning, whereas 30 to 40 mg. Vitamin B daily seemed to be satisfactory.

A commission had been appointed at the beginning of the war to study the toxicology of explosives. Dr. Keeser had in his possession the complete report of the commission and was ordered to destroy it sometime prior to the British occupation. For humanitarian reasons the order was never carried out. An abstract of this report, prepared by Dr. Keeser, is attached to this section.

Dr. Keeser also studied the problem of experimentally induced arteriosclerosis. His method of attack on this problem was suggested by the observation of some French scientists, that the artichoke contained an extractable substance that increased the solubility of cholesterol in blood. Dr. Keeser searched for other substances which might have the same qualities. In the dog, repeated injections of adrenalin, 1 mg. per day subcutaneously for six weeks, caused the establishment of a permanent hypertension. Concomitant administration of 100 mg. of sodium oleate daily prevented this effect of adrenalin. It was pointed out by a pathologist, that arteriosclerosis as induced was not comparable to the human type. Dr. Keeser therefore studied the chronic administration of lead salts, finding that 6 mg. daily of lead acetate per os produced an arteriosclerosis in dogs similar to the type observed clinically. This work is in progress at the present time.

Dr. Keeser also investigated the histamine content of liver extracts and the toxicity of some sulfonamides, including Marfanil.

Abstract of Professor Keeser's Report on Prophylaxis and Therapy of Health Hazards in Ammunition Workers.

This abstract was prepared because the report contains a considerable amount of information that can be found in any text book on organic chemistry.

1. Dinitrobenzene: The iron set free by destruction of erythrocytes is used by the organism again; for that reason iron treatment is of no value. While Vitamin B₁ is of no specific value it seems to act favorably on the general health of the workers. To combat impairment of liver metabolism ascorbic acid and yeast were tried prophylactically. Liver preparations were not successful. Dr. Keeser's claim that sodium thiosulfate acts favorably in dinitrobenzene poisoning has not been confirmed by other authors. In chronic poisoning B₁, C and glucose were used. Purine derivatives were given against headache. The latter favors the excretion of the poison.
2. Excessive work must be avoided, as increased respiration and perspiration augment absorption. Suitable protective clothing is necessary. Before eating, washing of face and hands is necessary, and after work a complete shower must be taken. Leather gloves and rubber aprons are necessary for the various manipulations.
3. First Aid and Treatment: Oxygen with 5% carbonic acid, a pulmotor and oxygen apparatus must always be available. The following medicaments must be ready for use: Glucose, camplon, B₁, S-Hydryl tablets, cardiazol, sympatol, lobelin, and phenobarbital.
4. Trinitrotoluene: Animal experiments showed no histological damage to the liver; the liver function, however, was impaired. Adrenalin hyperglycemia was prolonged.
5. Dinitroanisol: High dosage in cats causes paralysis of the respiratory center, also circulatory damage (paralysis of the capillaries and formation of exsudate). Alcohol increases the toxicity by 100%. Methemoglobin formation is not significant for the seriousness of the poisoning.
6. Mononitrobenzene: In acute poisoning cerebral symptoms prevail. Death occurs in coma with signs of circulatory failure. In prolonged poisoning hemolysis and formation of methemoglobin

lung damage with edema, circulatory failure, and severe gastro-intestinal disturbances with vomiting are present. In the urine is found p-aminophenol, excreted as sulfuric or glucuronic acid ester.

During recovery, relapses with cyanosis occur. Cardiac damage and general neurastenia may persist for some time, but permanent damage is rare. Changes in the retina with brown discoloration have been mentioned as diagnostically significant.

Chronic poisoning is rare and corresponds to the general symptoms of poisoning by organic nitrocompounds. Anemic and subicteric paleness are characteristic. Sensitization leads to dermatitis.

1) Poisoning with Chloronitrobenzene, nitrophenol, chlorodinitrobenzene, trinitrobenzene, nitrotoluene, and 2,4-dinitrotoluene.

These intoxications resemble nitrobenzene poisoning. Inspiration of large quantities of finely divided chloronitrobenzene may lead to severe nervous and psychic disturbances. Prolonged absorption of small quantities caused hypercytemia and increase of hemoglobin in the blood. The initial symptoms were vertigo, tiredness, cough, coryza, headache, then cyanosis, increased pulse rate, followed by anemia.

1.2.4. chlorodinitrobenzene is stronger than chloronitrobenzene and is especially irritating to the mucosa. It is eliminated as mononitroaniline.

2) Trinitrobenzene. No poisoning has been reported.

Nitrotoluene is less toxic but similar in action to the compounds described.

3) Dinitrobenzene is very dangerous. It is transformed into mononitroaniline.

Test: reduce urine with SnCl_2 , neutralize with NaOH and add NaNO_2 : a yellow color develops.

The general symptoms are the same as described for nitrobenzene. In women, disturbances of menstruation occur. Central disturbances in vision and hearing are observed. Fatal outcome is rare. In chronic poisoning, the nervous symptoms play a less prominent role. Changes in the blood and liver damage prevail. Damage to the optic nerve is relatively frequent and often persistent. Scotomata also occur. The nervous symptoms may last for a long time.

5) Trinitrotoluene has an outspoken effect on the liver in sensitive persons causing yellow atrophy. It is absorbed as dust or vapor by inspiration. It is eliminated through the lungs and urine as glucuronic acid compounds.

Test in the urine: Dil. 12.5 cc of urine with same vol. of dil. sulfuric acid (20 vol. H_2SO_4 and 80 water) and shake with 10 cc ether. Wash the ether with 25 cc of water and then mix with 5 cc of KOH in alcohol (5 KOH in 100 cc abs. alcohol). If trinitrotoluene is present, a pink to red color develops. The reaction is extremely sensitive. It does not prove that actual poisoning has occurred. Acute poisoning is practically unknown.

Chronic poisoning occurs only after a contact of at least a month. Symptoms are headache, bad taste, dryness in the mouth or salivation, loss of appetite and weakness. Local irritation is mostly due to the presence of tetrinitromethane. It appears as coryza, sneezing, epistaxis, conjunctivitis. Jaundice and liver damage are the most serious consequences. The urine contains bile pigments, protein and sugar. The simultaneous action of ammonium nitrate increases the toxic effect. Death occurs in coma with motor excitation. Somnolence followed by unconsciousness precede this stage. The circulatory effect is insignificant and the blood picture is not changed, except for an increase in eosinophils. The Takata-Ara reaction is positive. Total cholesterol is augmented with a decrease in the esters.

Loss of memory, visual disturbances, peripheral neuritis and, in women, psychic depression and excitation have been described. Death may still occur after apparent cure.

persons with gastric hyperacidity are more likely to show symptoms of poisoning. Dermatitis and eczema may develop. In severe cases the lymphatic system is involved. The prognosis is not unfavorable except in severe liver damage.

5) Nitroxylen, m-trinitroxylen and nitrophenol are similar to nitrobenzene in their action, but far weaker.

6) Dinitrophenol. The toxic effects have been studied extensively because of its use as a reducing agent. Technical poisoning has occurred only occasionally. It is absorbed as vapor or dust through the lungs, by ingestion and through the skin. Diseases of the liver, kidneys, and lungs, alcoholism, rheumatism predispose to intoxication. Symptoms: Increased respiration, pulse frequency, feeling of heat and sweating, thirst and loss of appetite. Increased BmR. Slight anemia may develop, but generally the blood picture is not changed. It may be found in the blood as follows:- Dilute the blood ten times and treat with tungstic acid and sulfuric acid to remove proteins. Alkalize with Na carbonate and compare the color of normal blood filtrate to which dinitrophenol has been added. Severe cases may develop agranulocytosis. The kidneys are usually not damaged. Determination in the urine by the method of A. Meyer. Death occurs in coma with convulsions, hydriasis and abolished reflexes. Cataract may be another consequence. Exanthema and exfoliative dermatitis with edema; loss of nails and hair may develop. The prognosis is unfavorable and the temporary improvement must be considered a danger sign.

Treatment: intake of much fluid, especially isotonic Na-Cl and glucose soln; cool baths.

7) Picric acid is less toxic. Symptoms of poisoning are irritation of the mucosae, skin irritations, gastric disturbances. Poisoning in industry is mostly caused by nitrous gas and not the picric acid. In addition to the direct staining effect there may be a true jaundice. Method of blood analysis: Mix 15 drops of blood with 3 cc of a 9.5% NaCl soln. and keep for 24 hours, shaking occasionally. Remove 1-2 cc of the top layer. A yellow color is significant for picric acid.

after mixing with an equal volume of methylene blue soln. (1:50,000) and shaking, add one hour later 10-15 drops of chloroform. After shaking, the chloroform is green, which does not appear in common jaundice.

Detection in urine: Acidify with sulfuric acid and place some natural silk or wool threads into the urine. After 24 hours the fibers show a yellow color that cannot be washed out. It is also possible to acidify with HCl and shake out with ether. Shake the latter with NaOH: the ether becomes colorless, the alkali red.

In a single case of acute poisoning which was reported there was a short period of unconsciousness with general malaise, followed by a hypochromic anemia. There was for a short time a relative lymphocytosis, diminution of the patellar reflex, increase of uropilinogen in the urine, and oliguria; gastric lavage produced crystals of the acid.

In chronic intoxications are found occasionally conjunctivitis and perforation of the nasal septum, more rarely bronchopneumonia develops. Severe cases show gastric and enteric symptoms, fever and neuritic signs (sciatic nerve) vertigo, convulsions, formation of methemoglobin. Eczema occurs especially often at hot temperature. The prognosis is favorable.

8) Hexanitrodiphenylamine. New workers generally develop acute skin inflammations and eczema, which, however, disappear within 10-14 days. Only especially sensitive persons are unable to work with the substance at all. General symptoms of chronic intoxication are: gastric disturbances, which are more severe than after trinitrotoluene, changes in the oral mucosa, stomatitis ulcerosa, and paradentosis. Some cases of myocarditis may be attributed to the intoxication, but this is not beyond doubt.

9) Tetranitromethylaniline. The general symptoms are similar to those described in the preceding paragraph. Some cases showed insomnia and vertigo, coryza, conjunctivitis, mild gastro-intestinal disturbances, icterus, in women menstrual disturbances. Severe damage does not seem to occur.

10) Organic Nitrates.

a Nitroglycerine.

Effects: Dilatation of the peripheral

and lowering of arterial pressure. Increase in heart action myocardial damage. Drop in body temperature. Methemoglobinemia, simultaneously formation of nitroxyhemoglobin and fotomethemoglobin. Poisoning by the vapor is extremely rare. Headaches, experienced during the first time of work with nitroglycerin usually disappear later. There seems to be an acquired tolerance.

b. Nitroglycol. The higher toxicity of this compound is due to its higher volatility, and ability to penetrate the skin. The first effect is a drop in blood pressure, especially systolic. (This is in direct contrast with the oral statement made by Dr. Keeser, namely that it has no influence on the blood pressure. A.E.M.). Large doses cause methemoglobin formation. smaller doses first the formation of 'Heinz' bodies. The changes caused in heart function are acceleration or slowing, and changes in the electrocardiogram. Pathological changes found are: myocardial, fatty degeneration of the heart, degeneration of the Ganglia at the base of the fourth ventricle and in the cerebellum. Liver damage was not observed, but occasionally an irritation of the blood-forming organs (Leucopenia, shift to the left, eosinophilia). Death has occurred especially during high summer heat. The acute poisoning leads to death with collapse, circulatory failure or anginal syndrome. In chronic cases headache and insomnia are the chief complaints. Excitation occurs, also cramps in the upper abdomen, loss of appetite, palpitations and menstrual disturbances have been reported, a low pulse pressure is quite common.

c Hexogen (Cyclotrimethylenetrione). Few cases have been reported. It is taken up as dust. Typical is the sudden onset of malaise and loss of consciousness. After vomiting improvement is felt. In experiments severe states of excitement and tonic-clonic convulsions were observed. The pathological changes were degenerative changes especially in the kidneys. It has also caused ulcerative dermatitis and stomatitis.

Preventive measures: Administration of glucose, vitamins and suitable nutrition. Workers with dinitrobenzene and TNT should receive 50 g. glucose in tea. Vitamin C must be given in doses of 100 mg., B₁ of 4 mg. daily. Good results were obtained with the preparation Dibionta. A product containing 30 mg. vitamin C, 4 mg. B₁, in addition the other factors of the B complex, calcium diphosphate and 0.3 g. glucose in one tablet is recommended.

Professor Dr. Keeser berichtet kurz über Untersuchungen zur Prophylaxe und Therapie von Gesundheitsschädigungen bei Munitionsarbeitern durch Sprengstoffe.

Ein allgemeiner Überblick über die Wirkungsweise moderner Sprengstoffe wird als Anlage 1 beigefügt.

Tierversuche, die zu neuen Kenntnissen über die Wirkungsweise von Sprengstoffen führten, werden im Sonderdruck Anlage 2 geschildert.

Ergänzende Bemerkungen über die Wirkungsweise von Sprengstoffen:

I. Dinitrobenzol:

Verabreichung von Eisen erwies sich als nutzlos, da bei dieser Vergiftung die Hauptmenge des beim Erythrocytenzerfall freiwerdenden Eisens dem Organismus nicht verloren geht (Versuch an Hunden).

Aneurin hatte ebenfalls keinen wesentlichen therapeutischen Erfolg. Eine prophylaktische Verabfolgung erscheint jedoch zweckmäßig um den körperlichen Status der Munitionsarbeiter zu haben. Weiter wurde in Tierversuchen gefunden, dass durch Dinitrobenzol der Leberstoffwechsel geschädigt wird. Daher wurde die prophylaktische Verabfolgung von Priovit (- Ascorbinsäure + Hefe) empfohlen. Die Behandlung mit Leberpräparaten und Eisen war bei erkrankten Arbeitern erfolglos. Die Verabreichung von Natriumthiosulfat, die sich mir zur Behandlung der Dinitrobenzolvergiftung als wertvoll erwiesen hatte, wurde von anderen Untersuchern, die allerdings ihre Hunde stets mit grossen Dosen Dinitrobenzol vergifteten, als nicht therapeutisch wirksam bezeichnet. Versuche am Menschen wurden meines Wissens nicht gemacht.

Bei der chronischen Vergiftung wurden Vitamin B₁ und C sowie Traubenzucker verabfolgt, ferner gegen die Kopfschmerzen Purinderivate, durch die auch die Ausscheidung des Ciftes beschleunigt wird.

Im allgemeinen wurden für die Vorbeugung gegen Dinitrobenzolvergiftung folgende Massnahmen angewandt:

1.) Allgemeine und spezielle technische Massnahmen zur Bekämpfung von Staub und Dämpfen:

Die einzelnen Arbeitsgänge sind nach Möglichkeit so einzurichten, dass schwere körperliche Arbeit vermieden wird. Durch die vertiefte Atmung und durch das Schwitzen bei körperlichen Anstrengungen wird die Aufnahme des Giftes in den menschlichen Körper begünstigt. Die Temperatur in den Arbeitsräumen ist möglichst kühl zu halten, da hohe Temperaturen die Vergiftungsgefahr erheblich steigern.

2.) Einzelschutz der Arbeiter:

Den Arbeitern wird Arbeitskleidung, bestehend aus Hose und Jacke, sowie Unterkleidung, bestehend aus Hemd, Unterhose, Fusslappen oder Strümpfen, zur Verfügung gestellt. Bei Arbeiten mit offenem Sprengstoff wird die Arbeitskleidung wöchentlich 2 mal, bei stärkerer Verschmutzung mit Sprengstoff sofort gewechselt und gereinigt. Ablegen der Arbeitsjacke oder Hochschlagen der Ärmel während der Arbeit mit offenem Sprengstoff ist zu vermeiden. Für die Arbeit mit offenem Sprengstoff werden Lederhandschuhe ausgegeben, deren Stulp möglichst den größten Teil des Unterarms bedeckt.

Vor jeder Nahrungsaufnahme sind Gesicht und Hände mit Wasser und SATINA (Fa. Heinr. Mack Nachf., Ulm a.d. Donau) zu-waschen. Nach jeder Arbeitsschicht wird geduscht. Satina wird in Seifenspendern zur Verfügung gestellt. Die Bade - und Duscheinrichtung ist so zu treffen, dass auf der einen Seite die schmutzige Arbeitskleidung abgelegt, dann geduscht und auf der andern Seite die saubere Strassenkleidung angezogen wird. In den Arbeitsräumen mit offenem Sprengstoff sind Waschbecken mit Satina-Seifenspendern anzubringen, damit die Arbeiter, die Sprengstoff an die Hände bekommen haben, sich reinigen können und nicht die Lederhandschuhe auf die beschmutzten Hände ziehen.

Bei dem Aufgeben des Sprengstoffs in den Misch- oder Schmelzkessel tragen die Arbeiter Gummi- oder Ölhandschürzen, Lederhandschuhe, Maske (z.B. Auer-Halbmasken mit Industrie-Sinsatz B). Die Masken sind gesäuert ausserhalb des Arbeitsraumes in geeignetem Behälter aufzubewahren.

In der Giessbox werden getragen: Lederhandschuhe und Gummibzw. Ölhandschürze.

Am Kühlkanal werden Lederhandschuhe getragen.

Bei dem Spiegelgiessen und Abschrauben der Giesstrichter werden Lederhandschuhe und Schutzschürze getragen. Sofern eine Absaugung nicht vorhanden oder nicht einwandfrei wirksam ist, wird eine Maske aufgesetzt. (Auer-Halbmaske mit Industrie-Einsatz B).

Bei dem Zerschlagen der Sprengladungen (Abnahme) werden Lederhandschuhe, -schürze und, sofern Absaugung nicht vorhanden, Halbmaske getragen.

Die Reinigung aller mit Sprengstoff verunreinigten Arbeitsgeräte und Gegenstände erfolgt mit heissem Wasser und Dampf möglichst im Freien. Handschuhe, Schutzhandschuhe und ggf. Halbmaske werden bei diesen Reinigungsarbeiten getragen.

Ernährung: Die Ernährung der Arbeiter soll kraftig und vitaminreich sein. Anträge auf Schwerarbeiterzulagen sind bei dem zuständigen Gewerbeaufsichtsamt zu stellen. Ferner ist für alle durch Sprengstoff gefährdeten Arbeiter Milch zu besantragen; mindestens 1/2 - 1 Liter Vollmilch pro Mann und Tag.

Als Ergänzungsstoffe zu der Ernährung werden Traubenzucker und ein Vitamin B₁-Präparat empfohlen.

3.) Erste Hilfe und ärztliche Betreuung:

Die Arbeiter des Dinitrobenzol-Betriebes sind ständig von einem Arzt zu überwachen.

Der Betrieb stellt einen ausgebildeten Heilgehilfen zur Verfügung, der von dem überwachenden Arzt über die besonderen Aufgaben der ersten Hilfeleistung bei Dinitrobenzol-Vergiftungen zu unterrichten ist.

Der Betrieb richtet einen Raum für die erste Hilfe und einen Raum für die ärztliche Untersuchung ein. Oft können die beiden Räume zu einem vereinigt werden.

Für die erste Hilfe sind außer dem üblichen Verbandmaterial zur Verfügung zu stellen:

Sauerstoff mit 5% Kohlensäurezusatz zur Beatmung Vergifteter.

1 Pulmotor-Gerät

1 Sauerstoff-Gerät

Das ärztliche Untersuchungszimmer ist so auszustatten, dass außer der allgemeinen auch eine genaue Untersuchung, insbesondere eine Mikroskopische und spektroskopische von Blut und Urin vorgenommen werden kann.

(Eine Aufstellung über die Einrichtung der ersten Hilfestelle und des ärztlichen Untersuchungsraumes wurde für die "Difa" gesondert ausgearbeitet.)

Für die ersten Behandlungsmassnahmen des Überwachungsarztes sind an Arzneimitteln bereit zu halten:

Graubenzucker in Substanz und zur Einspritzung

Campolon-Ampullen

Betabion, Tabletten und Ampullen

S-Hydril-Tabletten und Ampullen

Cardiazol-Ampullen

Sympatol-Ampullen

Lobelin-Ampullen

Luminal, Tabletten und Ampullen

Der überwachende Arzt hat die mit offenem Sprengstoff beschäftigten Arbeiter regelmässig zu untersuchen, sie an ihren Arbeitsplätzen aufzusuchen und sie in allen Vorbeugungsmassnahmen gegen Gesundheitsschädigungen durch Sprengstoffe zu unterweisen.

II. Trinitrotoluol.

Stärkere histologische Veränderung der Leber wurde im Tierversuch nicht beobachtet, dagegen ergaben Prüfungen der überfunktion, dass sie geschädigt ist. Die Adrenalin-Hyperglykämie zeigte einen verzögerten Ablauf.

III. Dinitroanisol.

In grossen Dosen verursacht es bei Katzen Lähmung des Atemzentrums und Lungenödem, ferner Kreislaufschädigung (Lähmung der Kapillaren mit Exsudatbildung). Alkohol steigert die Giftigkeit um mehr als das Doppelte. Die Methamoglobinbildung ist nicht massgeblich für die Schwere der Vergiftung.

1.) Mononitrobenzol. (C₆H₅NO₂)

Nitrobenzol (- Mirbanöl) ist eine farblose bis gelbliche Flüssigkeit mit starkem Lichtbrechungsvermögen. Sein Geruch erinnert an bittere Mandeln. Konzentrationen bis zu 0,04, mg/l sind mit dem Geruch noch wahnehmbar. Siedepunkt 208°, Erstarrungspunkt 3°. Die Dämpfe sind schwerer als Luft. Nitrobenzol ist wenig löslich im Wasser, gut löslich in organischen Lösungsmitteln. Technisches Nitrobenzol ist oft mit Nitrotoluol verunreinigt. Dämpfe entstehen vor allem dann, wenn es mit anderen Substanzen zusammen erhitzt wird. Die Aufnahme erfolgt in den meisten Fällen durch die Haut, öfters auch vom Magen aus, seltener durch Einatmung der Dämpfe. Ein grosser Teil des in den Organismus eingedrungenen Nitrobenzols wird unverändert mit der Ausatmungsluft durch die Lungen ausgeschieden. Mononitrobenzol ist vorwiegend akut giftgefährlich, insbesondere bei Unfällen bei denen die Arbeitskleidung mit Mononitrobenzol durchtränkt wird.

Bei der akuten Vergiftung stehen zerebrale Symptome im Vordergrund, der Tod erfolgt im Koma unter dem Zeichen der Kreislaufschwäche. Bei der protahiert verlaufenden akuten Vergiftung entspricht das Symptombild im Wesentlichen dem allgemeinen durch Nitroverbindungen verursachten Krankheitsverlauf. Im Vordergrund stehen in den schweren Fällen neben der Hämolyse und der Methämoglobinbildung Schädigungen der Lunge im Sinne eines Lungenödems, Kreislaufversagen- bzw.-schwäche und schwere Magen-Darmstörungen mit Erbrechen. Im Urin ist als Stoffwechselprodukt des Mononitrobenzols p-Amidophenol nachzuweisen,

das mit Schwefelsäure oder Glucuronsäure gepaart ausgeschieden wird. (Kpchen des Urins mit verdünnter Salzsäure, Nachweis durch die Indophenolreaktion)

Nach einer Besserung des Krankheitsbildes können akute Rückfälle mit erneuter Cyanose usw. auftreten. Als Folgeerscheinungen, welche die Rekonvaleszenz stark in die Länge ziehen, können lang anhaltende Anämien, Herzschwäche und allgemeine neurasthenische Erscheinungen bestehen bleiben. Dauerschäden sind aber nach akuten Mononitrobenzolvergiftungen sehr selten.

Differentialdiagnostisch sind von allen Herzerkrankungen, die mit starker Cyanose verlaufen, auszuschliessen. Der typische Bittermandelgeruch der Ausatmungsluft, manchmal auch des Urins wird manchmal auf die Diagnose hinleiten können, die durch den Nachweis von p-Amidophenol im Urin gestützt wird.

Von anderer Seite wurden Augenhintergrundsveränderungen mit dunkelbrauner Verfarbung und schokoladenfarbener Zeichnung der Netzhautgefässe (Zeichen der Methämoglobinbildung) bei der Mononitrobenzolvergiftung beobachtet und als brauchbares diagnostisches Symptom angegeben.

Die chronische Vergiftung ist selten, sie entspricht dem allgemeinen chronischen Vergiftungsbild durch aromatische Nitrokörper. Die chronischen Erkrankungen sind ausgezeichnet durch im wesentlichen anämische bzw. subikterische Hautblässe.

Disponierte Menschen können bei Beschäftigung mit Mononitrobenzol schwere Hauterkrankungen in Form von Rötung, Ödemen Ekzemen und pustulösen Erscheinungen bekommen, die u.U. ein Arbeitsplatzwechsel nötig machen.

2.) Vergiftungen mit Chlornitrobenzol und Nitrophenol und Chlordinitrobenzol. Trinitrobenzol. Nitrotoluol und 2,4 - Dinitrotoluol. -

Diese Vergiftungen verlaufen sehr ähnlich, wie die Nitrobenzolvergiftung. Eine ausführliche Beschreibung der Symptomatologie erübrigt sich deshalb.

Technisch werden die Chlornitrobenzol hauptsächlich in der Sprengstoffindustrie verwendet, vorwiegend in Form des sog. Tropföls, das ein flüssiges Gemisch von viel o- und weniger p-Chlornitrobenzol darstellt. Der Geruch des Chlornitrobenzols ist derselbe, wie der des Nitrobenzols: er erinnert an bitters Mandeln, ist jedoch intensiver und stechender. Die Chlornitrobenzole sind giftiger als Nitrobenzol. Die o-Verbindung ist giftiger als die Paraverbindung.

Die Aufnahme erfolgt durch Inhalation der Dampfe und durch Resorption durch die Haut.

Bei Einatmung grosser Mengen feinversprühten Chlornitrobenzols kann es zu schweren nervösen und psychischen Störungen kommen (Leymann). Bei wiederholter Einwirkung kleiner, an sich unwirksamer Dosen über längere Zeit hin wurde, ca. 2 Monate nach der Giftaufnahme eine mehrere Wochen bestehende, vorübergehende, reparative Hyperglobulie mit gleichzeitigem Anstieg des Blutfarbstoffgehaltes (Gerbis). Die Initialsymptome bestanden in Schwindel und Mattigkeit, dann stellen sich Husten, Schnupfen, starke Kopfschmerzen, vorübergehende Cyanose der Lippen und Stiche zwischen den Schulterblättern ein. Das Gesicht war stark gerötet, der Puls beschleunigt. Innerhalb kurzer Zeit hatte sich eine beträchtliche Anämie entwickelt. Die Erholung erfolgte langsam. Relativ lange bestand eine deutliche Dyspnoe. Die Hyperglobulie war erst zwei Jahre nach der Vergiftung verschwunden.

Chlordinitrobenzol ($C_6H_3 \cdot Cl \cdot (NO_2)_2$ (1,2,4,)). Es wirkt etwas starker als Chlornitrobenzol, unterscheidet sich von diesem jedoch durch die stärkere Schleimhautreizung und eine besonders starke Reizwirkung auf die Haut. Chlorinitrobenzol wird im Organismus in Mononitroanilin umgewandelt und so im Urin ausgeschieden (Nachweis siehe bei Dinitrobenzol).

Vom Trinitrobenzol ($C_6H_3 \cdot (NO_2)_3$), von dem zwei Isomere (1,3,5-Trinitrobenzol und 1,2,4,-Trinitrobenzol) existieren, sind Vergiftungen am Menschen bisher nicht bekannt geworden. Nach White und Hay wirkt es im wesentlichen nur weniger giftig als m-Dinitrobenzol.

Die Giftwirkung des Nitrotoluols ($C_6H_4 \cdot CH_3 \cdot NO_2$) ist sehr schwach qualitativ der der bisher beschriebenen Körper gleich. Die drei Isomeren, o-, p- und m-Nitrotoluol, von denen die o-, und p-Verbindung in den praktisch verwendeten Gemischen überwiegen, werden die letzteren in der Sprengstoff-, Munitions- und Teerfarbenindustrie verwendet. Die Aufnahme erfolgt durch Einatmung von Staub oder durch Tröpfcheninhala-tion. Bei langdauernder Arbeit und besonderer Disposition entwickeln sich Methämoglobinämie und Anämie. Ersters Schädigungen sind nicht auf die Wirkung des Nitrotoluols, sondern lang seine Verunreinigung mit Tetranitromethan zurückzuführen (Koelsch).

Von den verschiedenen Isomeren des Dinitrotoluols ($C_6H_3 \cdot CH_2 \cdot (NO_2)_2$) hat nur die 2,4-Verbindung gewerbliche Bedeutung. Man benutzt sie in der Sprengstoff- und Teerfarbenindustrie. Das klinische Symptomenbild ist das gleiche wie bei den vorbeschriebenen Vergiftungen mit anderen aromatischen Nitroverbindungen. In einem Fall traten nach Biergenuss akute Verwirrungszustände und Gedächtnisverlust auf (Friedländer).

3.) Dinitrobenzol.

Dinitrobenzol $C_6H_4 \cdot (NO_2)_2$ ist der bei weitem in der Herstellung sowohl als auch in der Verarbeitung gesundheitsgefährlichste Sprengstoff. Praktisch von gewerbehygienischer Bedeutung ist nur das m-Dinitrobenzol, die o- und p-Verbindung spielen technisch keine Rolle. Dinitrobenzol ist ein fester, in reinem Zustand farbloser und geruchloser Körper. Die Hautresorption steht bei Dinitrobenzol als Quelle der Giftwirkung im Vordergrund. Dinitrobenzol wird im Organismus zu Mononitroanilin abgebaut und so im Urin ausgeschieden.

Der Nachweis von Mononitroanilin im Urin erfolgt nach folgender Methode: Dem Urin, bzw. seinem Filtrat oder Ätherauszug wird Zinnchlorid unter Abkühlen zugesetzt und mit verdünnter Natronlauge neutralisiert. Beim Zusatz einiger Tropfen einer Natriummittritlösung entsteht bei Anwesenheit von Mononitroanilin eine geiß bis gelbbraune Verfärbung.

Dinitrobenzol ruft alle oben beschriebenen akuten und chronischen Vergiftungserscheinungen, einschließlich der Leberschädigungen in typischer Weise hervor.

a) Die akute Vergiftung.

Neben den im allgemeinen Teil aufgeführten Symptomen treten Verdauungsbeschwerden, bisweilen starkes Hautjucken auf, wozu in schweren Fällen in stärkerem Masse Beklemmungsgefühl auf der Brust, stärkere Kurzatmigkeit, Herzklopfen usw. als Zeichen eines leichten Sauerstoffmangels treten. Schwierigkeiten bei der Miktions sind nicht selten. Die objektiven Befunde (Kurzatmigkeit, Cyanose, Methämoglobinbildung, hämolytischer Ikterus, Blutveränderungen) sind oben beschrieben.

Bei Frauen setzen die Regelblutungen aus oder sind verstärkt und oft mit heftigen Schmerzen verbunden.

Am Zentralnervensystem kommt es infolge der schlechten Sauerstoffversorgung des Gehirns schon frühzeitig zu funktionellen

Sehstörungen, auch Anisokorie und Nystagmus wurden beobachtet (Floret), auch das Hörvermögen ist herabgesetzt. Der Gang wird unsicher und schwankend. Bisweilen besteht ein deutlicher Tremor. Sensibilität und Motilität bleiben meist intakt. Im Endstadium entwickelt sich ein komatöser Zustand mit den oben beschriebenen Symptomen.

Der tödliche Ausgang ist nicht sehr häufig. In den meisten Fällen kommt es zu einer raschen Besserung zumeist ohne längere Zeit überdauernde Restsymptome. Die Prognose ist im allgemeinen günstig.

b) Die subakute bzw. chronische Vergiftung.

Bei der chronischen Dinitrobenzolvergiftung treten die nervösen Erscheinungen, die bei der akuten Vergiftung recht ausgesprochen sein können, viel mehr in den Hintergrund. Die Blutveränderungen und in vielen Fällen auch die Leberschädigungen beherrschen das gesamte klinische Krankheitsbild.

Die anfänglichen Beschwerden sind wenig charakteristisch und wenig ausgeprägt, das Gesamtbefinden und der Appetit wenig gesort. Das volle Vergiftungsbild ist oben beschrieben.

Auffällig sind die gelegentlich auftretenden schweren Optikusschäden, die nicht selten für dauernd bestehen bleiben. Objektiv finden sich entzündliche Erscheinungen an der Sehnervenpille mit temporaler Abblässung derselben, manchmal auch zentrale Skotome.

In allen Fällen mit schweren Leberschädigungen ist die Prognose durchaus ernst, wenn nicht infaust, in den übrigen Fällen noch immer günstig. Bei der chronischen Dinitrobenzolvergiftung bleiben im Anschluss an die sehr langsam verlaufende Rekonvaleszenz allgemein nervöse Symptome sowie anämische Zustände zurück, deren Ausheilung längere Zeit erfordert.

An der Haut werden durch Dinitrobenzol knötchenförmige Ekzeme mit mehr oder minder starken Hautschwellungen beobachtet.

Dinitrobenzol ist die gefährlichste der in der Sprengstoffindustrie zur Verarbeitung gelangenden Nitroverbindungen, auch unter besten Betriebsverhältnissen ist mit dem Auftreten von Gesundheitsschädigungen zu rechnen.

4. Trinitrotoluol.

Reines Trinitrotoluol ($C_6H_5\cdot CH_3(NO_2)_3$) (2,4,6) bildet hellgelbe, im Licht allmählich nachdunkelnde, nahezu geruchlose Kristalle mit einem Schmelzpunkt von $82^\circ C$, die im Wasser kaum, in Benzol dagegen leicht löslich sind. Es existieren mehrere Isomeren. Technisches Trinitrotoluol, das gewerbliche Vergiftungen hervorruft, kann mehr oder minder mit Nitrobenzol, Kohlenwasserstoffen, Nitrosen Gasen und vor allem Tetranitromethan verunreinigt sein. Diese Verunreinigungen, namentlich die Beimengungen von Tetrinitromethan, sind nur während des Herstellungsprozesses von Trinitrotoluol vorhanden, durch die exakte Durchführung der vorgeschriebenen Reinigungsmethoden (Sulfitwäsche, strenge Abnahmebestimmungen) ist bei der Verarbeitung von Trinitrotoluol nicht mehr (z.Zt. Wenigstens) mit derartigen Verunreinigungen zu rechnen.

Da im Jahre 1940 bei der Verarbeitung von Tri. eine Zahl von Todesfällen an akuter gelber Leberatrophie aufgetreten ist und hierbei Verunreinigungen durch Tetranitromethan mit Sicherheit auszuschalten sind, kann die namentlich vom Weltkrieg her bekannte Streitfrage der Urheberschaft des Tetrinitromethans für die schweren Lebererkrankungen in dem Sinne entschieden werden, dass Trinitrotoluol selbst als reines Produkt die ausgesprochene leberschädigende Wirkung bei disponierten Menschen besitzt.

Die Aufnahme erfolgt in erster Linie durch die Einatmung von Staub (Pressverarbeitung) oder von Dampfen (Schmelzen, Abfüllung im flüssigen Zustand), also durch die Lunge. Die Hautresorption spielt nur eine untergeordnete Rolle.

Die Ausscheidung von Tri erfolgt z.T. durch die Lungen, z.T. durch den Harn in Form der Glucuronsäureverbindung des 2,6 Dinitro-4-tydroxylaminotoluols. Nachweis durch die Webstersche Probe.

12,5 ccm Harn werden mit der gleichen Menge verdünnter Schwefelsäure (20 Raumteile konz. Schwefelsäure mit 80 Raumteilen Wasser) gemischt und in einem Scheidetrichter mit 10 ccm Äther geschüttelt; die wässrige Flüssigkeit wird abgelassen, die zurückbleibende Ätherlösung mit 25 ccm Wasser gewaschen, dann in einem Reagenzglas mit 5 ccm alkoholischer Kalilauge (4-5 g Kaliumhydroxyd in 100 ccm abs. Alkohol) versetzt. Ist Trinitrotoluol vorhanden, so tritt je nach der Menge eine Rosa- bis Purpurfärbung auf. Die Ablesung muss schnell erfolgen, da vor allem bei schwach positiver Reaktion die Färbung bald in Braun übergeht. Die Reaktion ist ausser-

ordentlich empfindlich. Sie ist bei allen Arbeitern positiv, die mit Trinitrotoluol arbeiten, meist schon in der ersten Arbeitswoche, zuweilen erst nach 14 Tagen. Nach Aussetzen der Arbeit fällt sie einige Tage lang positiv aus. Ist die Reaktion auch ohne Zusatz von Schwefelsäure positiv, so war der Harn nur mechanisch durch beigemischtes Trinitrotoluol verunreinigt (nach Flury-Zernik, l.c.S.234).

Der positive Anfall der Websterschen Probe beweist nur die Aufnahme von Trinitrotoluol im Organismus, besagt aber nichts über etwa bestehende toxische Resorptionserscheinungen.

Ihr Wert ist damit für diagnostische Untersuchungen stark beschränkt und ihre Durchführung wird daher nur in Zweifelsfällen über die Natur der einwirkenden Nitroverbindungen weiterhelfen können, ferner kann mit ihr der Erfolg besonderer technischer Schutzmassnahmen und eines etwa veranlassten Arbeitsplatzwechsels kontrolliert werden.

Vereinzelt sei beobachtet werden, dass bei schweren Vergiftungen durch Trinitrotoluol sogar die Webstersche Probe negativ ausfiel. Kontrollbefunde sind hierzu notwendig.

Die akute Vergiftung durch Trinitrotoluol ist praktisch unbekannt. Akut verlaufende Vergiftungsfälle sind in Einzelfällen bei besonders empfindlichen und disponierten Menschen schon nach kürzerer Beschäftigungszeit zur Beobachtung gekommen, lassen sich aber in die Reihe der chronischen bzw. subakuten Trinitrotoluolvergiftung einordnen.

Die chronische Trinitrotoluolvergiftung.

Die Giftwirkung zeigt sich erst nach einem längeren Kontakt von mindestens einem Monat, zumeist nach einer Beschäftigungszeit von 2-4 Monaten. Die schweren Erkrankungen, die nur bei einer entsprechenden individuellen Disposition auftreten, beginnen nach den vorliegenden Erfahrungen mit grosser Regelmässigkeit im Zeitraum von 4-16 Wochen nach Beginn der Arbeitsaufnahme bzw. Berührung mit Trinitrotoluol.

Die Initialsymptome der chronischen Vergiftung bestehen in Kopfschmerzen, üblem Mundgeschmack, Mundtrockenheit oder Speichelfluss, Appetitlosigkeit, allgemeiner Schwäche; lokale Reizsymptome können insbesondere bei den mit der Herstellung von Trinitrotoluol und in der Sulfitwäsche beschäftigten Gefolgschaftsmitgliedern infolge der hier vorhandenen Verunreinigungen in erster Linie von Tetranitromethan im Vordergrund stehen.

Die Reizung der Luftwege äussert sich in Katarrhen der Nase und des Rachens, trockenem Husten und Kurzatmigkeit. Niesen und Nasenbluten treten auf, die häufig mit starken Stirnkopfschmerzen verbun-

den sind. Die Schleimhäute der Augen sind in einem Reizzustand. Bei der Einatmung von Staub, aber auch von Dämpfen stehen Reizsymptome von Seiten des Magen-Darmkanals oft deutlich im Vordergrund. Brechreiz und Erbrechen, Aufstossen oft auch Verstopfung. Flatulenz und Durchfall sind die am meistens geklagten Symptome. In manchen Fällen klagen die Kranken über qualende krampfartige Leibscherzen. Während die lokalen Reizsymptome, die sich auch an der Haut (siehe unten) zeigen können, im allgemeinen harmlos sind, aber sehr lästig und unangenehm empfunden werden, sind die resorptiven Erscheinungen sehr schwerwiegend und ergeben stets eine zweifelhafte Prognose. Es kommt in erster Linie zu schweren Schädigungen der Leber mit ikterischen Erscheinungen mit Auftreten von Gallenfarbstoffen und Bilirubin daneben von Eiweiss und Zucker im Urin bzw. erhöhten Bilirubinserumwerten. Die resorative Giftwirkung auf die Leber soll bis gleichzeitigem Einwirken von Ammonsalpeter gesteigert sein. Innerhalb weniger Tage, oft aber auch nach einer scheinbar kurz anhaltenden Besserung entwickelt sich das klinische Bild der subakuten bzw. akuten gelben Leberatrophie mit allen ihren tickischen klinischen Erscheinungen. (Ikterus, Bauchdeckenspannung, Verkleinerung der Leberdämpfung usw.) Bradykardie und Pruritus fehlen jedoch meist. Der Tod tritt im Koma hepaticum gelegentlich mit hochgradiger motorischen Unruhe, Somnolenz und schliesslich Bewusstlosigkeit ein. Vereinzelt wurde ein terminaler Ausgang der Trivergiftung unter dem Bild einer Agranulocytose beobachtet. Herz und Kreislauf sind wie die Lunge an dem grossen Krankheitsgeschehen wenig, höchstens sekundär, beteiligt. Manchmal treten Pulsunregelmässigkeiten auf. Blutdruck und Pulsfrequenz bleiben jedoch im allgemeinen bis an das Endstadium normal. Die Blutveränderungen sind gering. Typisch ist die Vermehrung der Heinz'schen Innenkörperchen. Methemoglobin ist kaum nachzuweisen. Beim protrahiertem Vergiftungsverlauf ist eine Anämie feststellbar. Im weissen Blutbild wird nicht selten anfänglich eine neutrophile Leucocytose, die aber rasch in die typische Leucopenie übergeht, beobachtet. Gleichzeitig damit tritt eine relative Lymphocytose auf. Eine Vermehrung der Eosinophilen wurde von verschiedener Seite beobachtet, in schweren Fällen treten subkutane und Schleimhautblutungen auf. Bei schweren Leberparenchymenschädigungen wird die Takata-Ara Reaktion im Serum positiv. Bilirubin ist im Serum direkt und indirekt stark vermehrt. Das Gesamtschleesterin ist stark erhöht und die Cholesterinester stark vermindert. (Estersturz). Am Zentralnervensystem finden sich keine typischen Symptome bzw. nur solche, die im Verlauf des Koma hepaticum auftreten.

Im Einzelfalle sind Gedächtnisschwäche, Sehstörungen, periphere Neuritis, bei Mädchen psychische Depressionen und auch Erregungszustände beschrieben.

Häufig treten Menstruationsstörungen mit unregelmässigen und verrinerten Regelblutungen auf. Es ist hierbei auch an die Wirkung der Orts- und Milieuänderung, besonders bei der Lagerunterbringung von Frauen zu denken, da wir ähnliche Erscheinungen auch bei nicht gesundheitsschädlichen Arbeitsprozessen häufig zu sehen bekommen.

Potenzstörungen bei Männern sind in Einzelfällen auf T. zurückgeführt worden (?)

Trinitrotoluol hat anscheinend eine besonders spezifische Wirkung auf das Leberparenchym. Das Einsetzen der Erkrankung ist oft wenig eindringlich, daher erfolgt das Aussetzen von der Arbeit oft zu spät bzw. wird nach einer anfänglichen Besserung die Wiederaufnahme der Arbeit zu früh gestattet. Es sind Spätodesfälle nach der Entlassung oder während des Urlaubs nach anfängliche leichten Erkrankungen mit rascher Besserung beobachtet worden, die zur besonderen Vorsicht mahnen müssen.

Bei Triarbeitern sind von verschiedenen Stellen Störungen der Magensaftsekretion im Sinne einer hypaziden Gastritis, selten einer hyperaziden Gastritis beobachtet worden.

Zunächst dachte man, dass Trinitrotoluol mit der Salzsäure des Magens schleimhautschädigende Verbindungen eingeht. Tri verhält sich jedoch indifferent gegenüber verdünnter Salzsäure. Dagegen erfolgt bei alkalischer Einwirkung ein rascherer Angriff, bzw. Abbau. Es wird daraus gefolgt, dass hypazide Menschen mehr gefährdet sind als hyperazide.

An der Haut treten unter lebhaftem Jucken und Brennen Erytheme, Quaddeln und Bläschen mit nachfolgender Abschuppung und langwierige nässende Ekzeme auf.

Sekundäre Lichenifikation wird beobachtet. Prädilektionsstellen sind Arme und Füsse und Reibungsstellen der Haut. Unreinlichkeit und Schweiß beginnen steigen das Auftreten von Hauterkrankungen. In schweren Fällen bei individueller Disposition sind sekundäre Entzündungen der Lymphknoten und Lymphbahnen beschrieben. Die Prognose ist bis auf die mit schweren Leberschädigungen einhergehenden Fälle durchaus günstig.

5. Vergiftungen durch Nitroxytol, m-Trinitroxytol und Nitrophenol.

Nitroxytol $C_6H_3(CH_2)_2NO_2$ und Trinitroxytol $C_2H_3(CH_2)(NO_2)_3$, die beide in der Sprengstoffindustrie keine oder nur eine unbedeutende Rolle spielen, wirken ähnlich wie das Mononitrobenzol, nur wesentlich schwächer.

Nitrophenol $C_6H_4OH NO_2$. Die p-Verbindung ist am giftigsten. Vergiftungen am Menschen sind bisher nicht bekannt geworden.

6. Vergiftungen durch Dinitrophenol.

Dinitrophenol $1,2,4\text{ C}_6\text{H}_3\text{OH NO}_2$ ist eine gelblichweisse, kristallini-
sche Substanz mit einem Schmelzpunkt von $113-115^\circ$, ist in Wasser
schlecht, gut in organischen Lösungsmitteln löslich. Obwohl eine um-
fangreiche Literatur über Vergiftungen mit Dinitrophenol besteht
(Abmagerungskuren!), ist die Zahl der gewerblichen Vergiftungen ge-
ring.

Das Vergiftungsbild ist stark abweichend von dem der Vergiftung
durch aromatische Nitroverbindungen.

Die Aufnahme erfolgt durch Einatmung von Dämpfen oder des Staubes,
der z.T. auch verschluckt wird und so auch bei Inhalation vom Magen-
und Darmkanal aus resorbiert wird. Bei stark schwitzenden Personen
spielt auch die Resorption durch die Haut eine nicht unbedeutende
Rolle. Leber, Nieren - und Lungenleiden, insbesondere Lungentuberku-
lose, Alkoholismus, Rheumatismus und Störungen der Wärmeregulation
steigern die Giftwirkung. Diese ist gekennzeichnet durch eine be-
trächtliche Steigerung der Gewebsoxydationen, verbunden mit einer
lebhaften Hyperthermie bis zu 40° Celsius und darüber, Atemnot
bei hochgradiger Beschleunigung der Atmung und der Pulsfrequenz bei
weichem, hüpfendem Puls. Subjektiv stehen neben dem Luftmangel ein
qualendes Wärmegefühl mit Schweißausbrüchen und Durstgefühl und Ap-
petitlosigkeit im Vordergrund. Bei chronischem Verlauf tritt starke
Abmagerung ein. Der Grundumsatz ist stark gesteigert. Auffallend ist
starke Cyanose, die im Gegensatz zur Vergiftung durch andere Nitro-
verbindungen nicht auf Methämoglobinbildung zurückzuführen ist, son-
dern auf eine Kohlensäureüberladung des Blutes. Beim, 1,2,4 Dinitro-
phenol fehlt im Gegensatz zu seinen Isomeren die Methämoglobinbildung
vollkommen, das Blut ist durch Nitrohämoglobinbildung auffallend
hellrot. Ausser leichten Anämien treten Blutveränderungen kaum auf.
Im Blut ist Dinitrophenol nachweisbar (Tainter-Wood).

Das zehnfach verdünnte Blut wird zunächst in der üblichen Wei-
se mit Wolframsäure und Schwefelsäure enteiweißt; das klare,
farblose Filtrat wird mit Natriumkarbonat alkalisch gemacht
und die auftretende Färbung der Lösung mit derjenigen ver-
glichen, die eine Lösung besitzt, die auf gleiche Weise aus
Normalblut mit einem bestimmten Dinitrophenolzusatz erhalten
wurde.

Milchsäure und Azetonkörper sind im Blut vermehrt nachzuweisen, die
Alkalireserve ist vermindert. In mehreren Fällen sind Agranulocyten
beobachtet worden. Gastrointestinale Störungen sind nicht erheblich,
schwere Leberschädigungen fehlen. Eine zuweilen feststellbare gelbe
Hautverfärbung ist nicht hepatzellulärer oder hämolytischer Genese,
sondern durch die Ablagerung gelber Dinitrokörper in der Haut zu er-

klären. Schädigungen der Nieren fehlen. Vereinzelt sind Cystitiden mit Albuminurie und Hämaturie beobachtet. Die Ausscheidung erfolgt in Form von Aminonitro- oder Diaminophenol sehr rasch, der Nachweis im Urin erfolgt nach der Methode von A. Meyer :

Der Urin wird mit neutralem Bleiacetat geklärt, mit Zinkstaub und Schwefelsäure bis zur völligen Entfärbung reduziert. Zu dem Filtrat werden einige Tropfen einer mit Schwefelsäure angesäuerten Kaliumbichromatlösung zugesetzt. Die Anwesenheit von Dinitrophenol ist an der auftretenden Rotfärbung zu erkennen. Zur genaueren Untersuchung werden nach anderer Vorschrift (vgl. Flury-Zernik S. 434) 10 ccm Urin mit 1 ccm 10%iger Schwefelsäure und 1 ccm, 0,5%igem Natriumnitrit versetzt und die Mischung 15 Minuten im Dunkeln stehen gelassen. Dann wird sie mit 10 ccm Aether ausgeschüttelt. Violette Farbung des Aethers zeigt die Anwesenheit von-, weinrote von p-, goldgelbe von o-Aminonitrophenol an.

In der schweren Fällen vor allem treten von seiten des Zentralnervensystems Bewusstlosigkeit, Koma, motorische Unruhe, gelegentlich auch schwere Krämpfe ein. Der Tod erfolgt im Koma unter Krämpfen bei Mydriasis und schliesslich erloschenen Reflexen. Bei peroraler Aufnahme sind schwere Linsenerkrankungen (subkapsulare Trübungen) mit darauf folgender Erblindung häufig.

Durch Dinitrophenol werden neben allergischen (Eosinophilie, Fieber), maculo-papulösen und urticariellen Exanthemen auch, schwerste exfoliative Hautveränderungen mit starken Ödemen, Gewebsaftabsonderungen, Verkrustungen, Nagel- und Haarverlust beobachtet, die zu schweren und schmerzhaften Hautkontrakturen führen können. Die schweren Vergiftungen haben eine infauste Prognose, vorübergehende Besserung und das Auftreten einer Euphorie gelten als ungünstiges Zeichen. Eine spezifische Therapie fehlt, am wirksamsten ist noch die reichliche Zufuhr von Flüssigkeit in Form von isotonischer Kochsalz- oder Traubenzuckerinfusionen, Dauertropfeinläufen oder Hypodermoklysmen sowie kühle Bäder heben den anderen therapeutischen Maßnahmen, die allgemein für die Vergiftung durch aromatische Nitroverbindungen beschrieben sind.

Vergiftungen durch die anderen Isomeren des Dinitrophenol verlaufen grundsätzlich anders, sie ähneln dem allgemeinen oben beschriebenen Vergiftungsbild durch aromatische Nitroverbindungen. Praktisch werden sie kaum zur Beobachtung kommen.

7.) Vergiftungen durch Pikrinsäure (Trinitrophenol).

Trinitrophenol $C_6H_2OH (NO_2)_3$ ist zu 1% wasserlöslich und schmeckt

stark bitter. Trinitrophenol ist einer der am wenigsten gesundheitsgefährlichen Sprengstoffe.

Die bei gewerblicher Vergiftung auftretenden Krankheitserscheinungen sind charakterisiert durch Reizung der Schleimhäute (Schnupfen, Niesreiz, Hustenreiz), Hauausschläge und Magenbeschwerden, sie sind im allgemeinen harmlos. Bei Vergiftungen schwerer Natur während der Nitrierung und Wäsche handelt es sich meist nicht um Trinitrophenolvergiftungen, sondern um die Einwirkung nitroser Gase.

Die Haut der Pikrinsäurearbeiter ist typisch gelb verfärbt, insbesondere im Gesicht, an den Händen und Unterarmen, ebenso zeigen die Kopfhaare, besonders der Stirnpartien vorwiegend bei blonden Personen, eine gelbrötliche Verfärbung. Es kann aber auch zu dem durch allgemeine Gewebsverfärbung verursachten, allergischen Pikrinikterus kommen, bei dem auch die Skleren gelb verfärbt sind. Dieser Pikrinikterus hat mit echtem Ikterus nichts zu tun. Dasgelegentlich auch Selbstvergiftungen vorkommen können, wird zur Differentialdiagnose die Methode der Blutuntersuchung auf Pikrinsäure angeführt.

Hierzu werden 15 Tropfen Blut mit 3 ccm einer 9,5%igen Kochsalzlösung versetzt und unter wiederholtem Schütteln 24 Stunden bei Zimmertemperatur stehen gelassen. Werden dann 1-2 ccm dieser Lösung abgehobert und ist diese auch nur schwach gelb gefärbt, so ist der Nachweis der Pikrinsäure erbracht. Setzt man die gleiche Menge einer Methylenblaulösung (1: 50000) zu, schüttelt und fügt nach einer Stunde 10-15 Tropfen Chloroform hinzu und schüttelt aus, so zeigt das Chloroform eine hellgrüne bis flaschengrüne Verfärbung, was bei gewöhnlichem Ikterus nicht der Fall ist.

Auch im Harn ist der Nachweis von Pikrinsäure leicht möglich.

Legt man einen ungefärbten Seiden- oder Wollfaden 24 Stunden lang in den mit Schwefelsäure leicht, angesäuerten Harn, so wird er in Anwesenheit von Pikrinsäure gelb; eine Entfärbung des Fadens tritt auch nach längerem Wässern nicht mehr ein (Koelsch). Man kann auch den Harn mit Salzsäure ansäuern, mit Äther ausschütteln und zu dem gelben Atherauszug etwas Natronlauge hinzufügen. In Gegenwart von Pikrinsäure wird der Äther farblos, die Lauge rot. Nach peroraler Aufnahme grosser Pikrinsäuremengen wechselt der Urin nach längerem Stehen in auffälliger Weise seine Farbe; dieser Farbenumschlag beruht auf Reduktion der Pikrinsäure in die viel giftigere Pikraminsäure (Pohl). Bei einer gelegentlich beschriebenen akuten Vergiftung durch Pikrinsäure wurde bei einer 18-jährigen Munitionsarbeiterin, die in einer Wolke von Pikrinstaub geraten war, nach einer kurzen Bewusst-

losigkeit bei allgemeinen Beschwerden eine mässige hypochromen Anämie gefunden. Über eine kurze Zeit bestand eine relative Lymphocytose, Abschwächung der Kniestehnenreflexe, Unrobilinogenvermehrung im Urin, Oligurie. Die Magenausspülung förderte massenhaft Pikrinsaurekristalle zu Tage.

Bei chronischen Vergiftungen wurden gelegentlich Conjunctivitiden und Nasenscheidewandperforationen, selten Bronchopneumonien beobachtet. In schweren Fällen traten gastrische und enteritische Symptome, Fieber und neuritische Erscheinungen (N. ischiadicus), Schwindel, Krämpfe, Muskelkontraktionen und Methämoglobinbildung hinzu.

Bei Frauen wurden Regelstörungen und zeitweilige Amenorrhoe beobachtet. In einem Fall wurde ein Abortus auf die Beschäftigung mit Pikrinsäure zurückgeführt (?).

An der Haut treten häufiger als bei Trinitrotoluolarbeitern besonders im Sommer und bei starker Hitze mehr oder minder ausgeprägte brennende, juckende, nässende und blaschenförmige ekzematöse Veränderungen auf; in manchen-Fällen bestehen schwere Toxicodermien mit Rötung und ödematischer Schwellung der Haut, Erscheinungen, die von Fieber und schwerem allgemeinen Krankheitsgefühl begleitet sind. Die Prognose ist durchweg günstig.

Bei etwa zur Beobachtung kommenden Selbstvergiftungen sollen neben den anderen therapeutischen Massnahmen Magenspülungen durchgeführt und milde Abführmittel gegeben werden.

8. Vergiftungen durch Hexanitrodiphenylamin und Tetranitromethylanilin.

Hexanitrodiphenylamin $(NO_2)_3 C_6H_2N \cdot C_6H_2 (NO_2)_3$

Zu Beginn der Beschäftigung mit Hexa erkrankt ein grösserer Prozentsatz der Gefolgschaft an akuten Hautentzündungen in Form von papulösen Akzemen, vorwiegend an den Händen und im Gesicht. Diese Hautreizungen klingen im allgemeinen nach 10-14 Tagen ab und rezidivieren nicht mehr. Bei disponierten Menschen kann es jedoch einerseits zu sehr schweren Dermatitiden, auch zu generalisierten Ekzemen kommen, die eine sehr lange Ausheilungszeit beanspruchen, andererseits können aber auch dauernde Rückfälle ein Arbeitsplatzwechsel notwendig machen.

Die allgemeine Giftigkeit von Hexa wurde zunächst als gewerbehygienisch bedeutungslos angesehen. Neuere Erfahrungen jedoch ergaben in einem immerhin erheblichen Prozentsatz der mit Hexa Beschäftigten, neben den Hauterkrankungen ein häufiges Auftreten von erheblichen Magenbeschwerden, die starker als bei Trinitrotoluol auftreten. Weiter

wurden Mundschleimhautveränderungen im Sinne einer Stomatitis ulcero-sa und Parodontose beobachtet.

Es besteht auch der Verdacht in einem Falle, dass Herzveränderungen im Sinne einer Myocarditis bei der Arbeit mit Hexa in Zusammenhang gebracht werden können(?)

Auch allgemeine Übelkeits- und Mattigkeitssymptome wurden beobachtet.

Tetranitromethylanilin. $C_6H_2(NO_2)_3 \cdot N \cdot NO_2CH_3$.

Auch bei Tetryl steht die hautreizende Wirkung ähnlich den oben beschriebenen Veränderungen im Vordergrund. Die unbedeckten Hautpartien sind gelb verfärbt, ebenso die Haare. An allgemeinen Erscheinungen wurden bei Tetrylarbeitern vereinzelt Schlaflosigkeit und Schwindel, Schleimhautreizungen (Schnupfen, Bindehautreizungen) häufiger leichte Magen-Darmstörungen, die besonders bei Frauen während der Menstruation auftreten und im einzelnen Falle auch ein Ikterus beobachtet. Schwere Schädigungen sind nicht zu befürchten.

III. Organische Salpetersäure-Ester.

1.) Nitroglycerin. $C_3H_5(ONO_2)_3$ ist eine völlig geruchlose Flüssigkeit, wenig wasser- aber gut fettlöslich. Nitroglycerin verdampft ziemlich leicht (schon bei gewöhnlicher Temperatur), die wesentliche Wirkung ist eine Nitritwirkung.

1. periphere Blutgefäßweiterung und Absinken des Blutdruckes
2. Beschleunigung der Herzaktion, u.U. Myocardenschaden
3. Absinken der Temperatur durch Wärmeverlust
4. Methamoglobinbildung, daneben Bildung von Nitroxyhemoglobin und Fotomethamoglobin. Eine akute Vergiftung durch die Einatmung von Dämpfen ist sehr selten.

Zu Beginn der Beschäftigung mit Nitroglycerin können anfänglich allgemeine Beschwerden, insbesondere stärkere Hinterkopfschmerzen, auftreten. Zumeist lassen diese anfänglichen Beschwerden bald nach und verschwinden völlig. Eine Gewöhnung ist anzunehmen. Bei Überempfindlichen kann auf Grund dieser Beschwerden, die dann bestehen bleiben, ein Arbeitsplatzwechsel notwendig sein.

2. Nitroglycol. (Äthylenglycoldinitrat) $(ONO_2)CH_2-CH_2 - (ONO_2)$.

Infolge einer wesentlich stärkeren Giftwirksamkeit und der ganz erheblichen, etwa 100 fach höheren Flüchtigkeit, aber auch des besseren Hautdurchdringungsvermögens ist die gewerbliche Giftgefährdung

bei den Nitroglycolen beträchtlich höher als bei Nitroglycerin. Im Vordergrund steht ein Absinken des Blutdrucks und zwar in erster Linie des systolischen Blutdrucks, das bei Arbeitsunterbrechung rasch zur Norm zurückgeht (in leichten Fällen auch während der Wochenendpause). Nitroglycol ist ferner ein starkes Blutgift. Bei der Einwirkung stärkerer Dosen ist die Methämoglobinbildung deutlich nachweisbar. Bei der Einwirkung kleinerer Dosen ist lange vor der Herzveränderungen (Beschleunigung oder Verlangsamung der Pulszahl, Veränderungen des Elektrokardiogramms) festgestellt worden. Pathologisch-anatomisch wurden Herzmuskelveränderungen und Herzverfettung neben Schädigungen der Gehirnsubstanz in Form von Ganglienzellendegenerationen an der Basis des vierten Ventrikels und am Kleinhirn festgestellt. Eine leberschädigende Wirkung der aromatischen Nitroverbindungen wird nicht beobachtet, während gelegentlich eine Reizwirkung auf die blutbildenden Organe (Leucopenie und Linksverschiebung, insbesondere auch Eosinophilie) beobachtet wurde. Todesfälle durch Nitroglycol sind, besonders in Amerika, aufgetreten. Auffällig war der Zusammenhang mit der heißen Jahreszeit und die Häufung der tödlichen, sehr rasch verlaufenden Erkrankungen über die Zeit des Wochenendes bzw. des Montags. Diese akut verlaufenden Fälle führten unter dem Bild einer schweren bedrohlichen kollapsartigen Kreislaufschwäche oder einer Angina pectoris oft in kurzer Zeit (extrem in wenigen Minuten) zum Tode. Bei der mehr chronischen Einwirkung stehen die schon beschriebenen Symptome im Vordergrund, an subjektiven Beschwerden wird ein der Hauptsache über Kopfschmerzen, besonders im Hinterkopf, und Schlafstörungen geklagt. Ebenso wie bei der Beschäftigung mit Nitroglycerin treten diese Beschwerden am stärksten bei Beginn der Beschäftigung auf. Im Einzelfall sind auch Erregungszustände bzw. erhöhte Erregbarkeit beschrieben worden. Im weiteren wird über Appetitlosigkeit, gelegentlich auch über häufige krampfartige Schmerzanfälle in der Magengegend geklagt. Herzsensationen und Regelstörungen bei Frauen werden häufiger angegeben. Gelegentlich wurde eine subacute Gastritis gefunden; ob sie als eine typische Folge der Nitroglycolvergiftung aufzufassen ist, kann nicht entschieden werden, dagegen ist die sehr häufig festgestellte geringe Blutdruckamplitude mit Nitroglycolbeschäftigung in Zusammenhang zu bringen.

III. Hexogen. Cyclotrimethylennitroamin.

Die Erfahrungen über Vergiftungen durch Hexogen sind nicht sehr gross. Die Aufnahme erfolgt in erster Linie durch die Einatmung von Staub. Typisch ist das Auftreten von plötzlichem Unwohlsein, begleitet von anfallweise auftretender Bewusstlosigkeit. Nach Erbrechen tritt Beserung ein. Sowohl an Menschen- wie auch im Tierversuch sind schwere Erregungszustände beobachtet worden. Die Krampfanfälle äussern sich

in lebhaften tonisch-klonischen Krämpfen. Im Tiersversuch wurden bei tödlichen Vergiftungen pathologisch-anatomische Veränderungen in erster Linie der Niere, ebenso degenerative Erscheinungen an anderem Organen beobachtet. Klinische Erfahrungen stehen hierüber noch aus. Durch Hexogen sind bei Überempfindlichkeit schwere Hauterkrankungen aufgetreten in Form ulzeröser Dermatitis; auch schwere Schleimhautschädigungen mit dem Bild einer Stomatitis ulcerosa wurden beobachtet.

Krankheitsvorbeugung durch betriebsärztlich gelenkte Gaben von Traubenzucker und Vitaminen und durch Ernährungsmassnahmen.

Die Dringlichkeit dieser prophylaktischen Massnahmen muss sich nach dem Gefährdungsgrad der jeweiligen Arbeit richten. In erster Linie sind Dinitrobenzol- und Trinitrotoluolarbeiter zu berücksichtigen.

Traubenzucker wird am besten in Tee, der mit Traubenzucker gesüßt ist verabreicht. 50 gr.tgl. sind im Allgemeinen hinreichend. Vitamin C muss nach den vorliegenden Erfahrungen in der Menge von ca 100 mg, Vitamin B₁ in der Menge von ca 4 mg tgl gegeben werden, um eine hinreichende Schutzwirkung zu erzielen. Gute Erfahrungen wurden mit dem Präparat Dibionta gewonnen, jedoch ist die Liefermöglichkeit dieses Präparates z.Zt. beschränkt. Dagegen ist die Bezugsmöglichkeit im Rahmen einer umfassenden Viteminaktion z.Zt. für das Präparat Vitemultin sichergestellt, das neben 30 mg Vitamin C ca 4 mg B₁, zuzüglich des übrigen Vitamin-B-Komplexes, Calciumbiphosphat und 0,3g Traubenzucker in einem Vitemultinplättchen (Preis: 2,2 Pfennig) enthält.

C. Interview with Dr. J. Kühnau, Professor of Biochemistry, Medical Faculty, University of Hamburg.

During the war Dr. Kühnau carried out research on the following subjects:-

1. The evaluation from a nutritional viewpoint of a synthetic vitamin A preparation (Vogen by Merck), which was found to be nearly equivalent to natural Vitamin A.
2. The value of synthetic Vitamin E (Hoffman-La Roche), in the treatment of progressive muscular dystrophy. Good results were claimed.
3. The use of synthetic Vitamin B in nutrition, and a search for natural sources of the Vitamin B complex.

4. Tetany resulting from calcium deficiency induced by the administration of guanidine derivatives to dogs, and the treatment thereof with parathyroid hormone.

5. The use of Vitamin B complex to control diabetes in partially depancreatized dogs.

6. Observations in connection with the effect of inositol on intestinal peristalsis.

7. The prevention of lead poisoning in humans by the use of riboflavin and/or nicotinic acid.

Dr. Kühnau has been in Hamburg for four years.

D. Interview with Professor Dr. Rudolf Mond, Professor of Physiology, Medical Faculty, University of Hamburg.

Professor Mond has devoted most of his time and effort to studies of cell permeability, with particular reference to the relationship of red blood cell structure and permeability. In studies on frog muscle he found that insulin could increase the permeability of muscle fibers to glucose, whereas adrenalin had the opposite effect. The alterations in permeability were observed when the glucose concentration was below the critical level of 40 mg. per cent. The work is not conclusive, but may be of theoretical interest. During the war, Professor Mond also conducted some studies with reference to the permeability of skin to some sodium chloropropionates, but the results were very indefinite..

Professor Mond has been at Hamburg for eleven years.

E. Interview with Professor H. H. Berg, Professor of Internal Medicine, Medical Faculty, University of Hamburg.

Professor Berg was interrogated at considerable length regarding possible advances in internal medicine. Professor Berg was highly cooperative, but it was evident that little progress in this sphere has been made in Germany in the last six years. He emphasised the difficulties imposed on medicine by the Nazi system and by bombing. The only positive points elicited were:-

1.) German physicians have increased their knowledge of louse-borne typhus, but without achieving any notable advance.

2.) Eyer and Brix have developed a rapid slide method of doing the Weil-Felix reaction using whole blood. This method might be of value in Scrub Typhus. The agglutinations are performed on prepared celluloid strips which can readily be carried in the pocket. (See Appendix II). Professor Berg spoke highly of the practical value of this simple method. It should be evaluated by a bacteriologist, who should keep in mind that under jungle conditions where scrub typhus occurs, laboratory facilities are often lacking, and a practical simple method, even though of very rough accuracy, would be a valuable aid.

Professor Berg stated that the chief shortages in Germany from the point of view of internal medicine, are of sulphapyridine, sulphathiazole and sulphaguanidine for oral use; sodium citrate; morphine derivatives; atropine; insulin; liver extracts; anaesthetics and X-ray films.

3. Institut für Schiffs- und Tropenkrankheiten.

This Institute, founded in 1900, is the chief center for the study of Tropical Medicine in Germany. The only other center, the Tropen - Genesungsheim at Tübingen, is of minor importance. Before it was bombed, it consisted of a fine building for teaching and research with an attached hospital of 80 beds.

The main division are as follows:-

Protozoology	:	Professor E. Reichnow
Helmiathology	:	Professor H. Vogel
Bacteriology	:	Dr. Lippelt
Entomology	:	Professor Martini (whereabouts unknown) Dr. Weyer
Pathology and Virus diseases)	Professor Nauck and Dr. Loos
Chemistry and Biochemistry)	Dr. Weise
Clinical	:	Dr. W. Mohr.

The work of the Institute during the war has been hampered by severance of contact with the tropics (except the Balkans and N. Africa), and by the destruction of premises in 1943.

The Institute was formerly located at Bernard Nocht Strasse No. 74, Hamburg, but has been almost completely destroyed. Only two small wards and a clinic are operating at this address. The other departments have been removed to Langenhorn, and the Hammerland Strasse No. 207.

The chemical and parasitological laboratories, and the library functioning at the Hamme land Strasse address were slightly damaged. Clinical work is being done at Langenhorn, and the buildings there are intact. Due to the destruction of the old Institute and its equipment, the necessity of moving to new locations, and the loss of key personnel due to the war, very little original work has been done in the past few years. Professor Dr. Nauck, Director of the Institute, is interested primarily in the virus diseases, but also has a broad knowledge of tropical diseases. Dr. Nauck believes that there has been no material advance in the treatment of malaria since the introduction of atebrin and plasmochin. He considers chemotherapy of typhus to be of little value. He recommends Yatren and emetine for amoebic dysentery, marfanil and sulfanilamide for tropical ulcer, and bacteriophage and sulfapyridine for bacillary dysentery.

Dr. Mohr, Chief of Clinical Medicine.

Malaria: Dr. Mohr has had considerable experience in the treatment of malaria with atebrin and plasmochin but his knowledge regarding these drugs compares unfavorably with that of matriologists in Britain and the United States. His information is particularly scanty regarding absorption, excretion, and blood levels obtained with different doses. He has also had limited experience with sontochnin. Dr. Mohr believes that the earliest relapses in vivax malaria occur 24 to 28 days after the end of treatment with either atebrin or sontochnin. He thinks that the relapse rate after sontochnin is somewhat lower than that following atebrin. His scheme of dosage with atebrin is 0.3 grams daily for five to seven days. He gives sontochnin in double the dose i.e., 0.6 grams daily for five to seven days, and believes that the tolerance of sontochnin is superior to that of atebrin. The only symptoms of toxicity which he has noted following sontochnin are mild gastro-intestinal symptoms in about 1% of the cases treated. For relapsing vivax malaria Dr. Mohr recommends quinoplasmin. He recommends three tablets daily for twenty-one

days. He demonstrated a patient who had had seven relapses of vivax treated by atebrin. This patient was at present on the quinoplasmin treatment. A second case of vivax malaria was demonstrated. This patient had been acutely ill, and gastrointestinal symptoms due to malaria had been pronounced. The patient was jaundiced upon examination, when admitted. This patient was treated by atebrin and plasmochin parenterally. He was given 0.3 grams of atebrin and 0.01 grams of plasmochin in the same injection, intramuscularly, daily for the first three days. After this, the patient's condition had improved to such an extent that he could be treated by oral medication. He was then given the usual doses of atebrin by mouth. Two cases of falciparum malaria, both quite severe, were demonstrated. One of these cases had been treated by intramuscular injections of 0.3 grams of atebrin mucinate daily, for two days, followed by 0.3 grams of atebrin daily for an additional seven days, by mouth. This patient appeared to be doing well. The second falciparum case not quite as severe as the first, had been treated by atepe tablets administered orally. Three tablets were given daily for seven days (one tablet of atepe contains 0.1 grams of atebrin and 0.005 grams of plasmochin). This patient was also recovering nicely. Dr. Mohr concedes the increased toxicity of atebrin and plasmochin administered concurrently, but believes that the added risks are justified in the treatment of severe cases. In addition to these specific remedies, Dr. Mohr usually administers reduced iron and Vitamin C to malaria patients. He does sedimentation rates on all serious cases, believing that repeated sedimentation rate on all serious cases, believing that repeated sedimentation rates give valuable information if the rate remains high during the remission, an early relapse is likely.

Kala azar: Dr. Mohr has seen a number of cases of Kala azar during the war in soldiers returning from the Mediterranean Theater. He has used both of the new I.G. Farben preparations of solustibosan, i.e., solustibosan concentrated, and solustibosan in oil. He believes that solustibosan concentrated is superior to the dilute preparation both from the standpoint of tolerance and of activity. Inasmuch as the concentrated preparation contains older preparation, larger doses can be given with the production of pressure pain. The intramuscular injections are therefore less painful. He also thinks that the preparation is more active than dilute solustibosan, even taking into consideration the difference in antimony content. In other words, he believes that 100 milligrams of antimony administered in a concentrated solution produce better results than the same amount

why this should be so. The treatment which he recommends for kala azar is to begin with 0.5 cc. at first, increasing the amount by 1/2 cc. each the fifth day. He has given as many as two such five-day courses in three weeks. He also claims to have given 1 cc. of solustibosan concentrated every twelve hours for six days; regardless of the type of initial treatment, and believes that all patients should receive a course of solustibosan in oil about six months after the first course of treatment. In the case of solustibosan in oil, he gives 5 cc. doses intramuscularly on alternate days for a fortnight.

Amoebic dysentery: Dr. Mohr has treated a number of cases of amoebic dysentery in soldiers returning from the North African and Eastern fronts. He has no improvements to offer on the standard treatment. In fact, the treatment which he uses is definitely inferior to that employed in both the British and American armies. He employs Yatren by enema in doses of 1, 2 and 3 grams dissolved in 5 cc. of water, for intestinal lesions, especially those in the lower colon; he recommends emetine for liver lesions. He was questioned regarding relapses, and admitted that many relapses occurred, but he did not at any time mention the use of emetine in bismuth iodide. Presumably this was unobtainable in Germany during the war. For prevention of spread of amoebic dysentery in wards, Dr. Mohr had nothing to offer and used only standard procedures for disinfecting excreta, etc. He has used a yatren-like preparation made by the I.G. Farben during the war, and this contained chlorine instead of iodine in the formula. He found it less effective and less well tolerated than Yatren.

Bacillary dysentery: Dr. Mohr has used bacteriophage for the treatment of this disease but says that action is too erratic. Some cases respond dramatically while other show no improvement whatever. He believes bacteriophage treatment is now superceded by sulfonamide drugs. He prefers sulfapyridine used in ordinary doses.

Pappatacci Fever: Dr. Mohr says that the Wehrmacht had excellent results in the prevention of Pappatacci Fever by impregnating mosquito nets with D.D.T. He knows of no treatment for this disease.

Typhus Fever: Originally twenty-five cases of typhus had been admitted to the hospital under Dr. Mohr's care. Twenty were still under treatment when visited and were demonstrated. Five cases had died. All twenty-five cases were members of the Wehrmacht and all had been vaccinated. All fatal cases were elderly i.e., all were over fifty years of age. The Weil-Felix reaction was positive in all cases in dilution of 1:200 up to 1: 6500.

Dr. Mohr believes that a diagnosis can be made on the fifth or sixth day by means of the Weil-Felix reaction. The course of all cases was typical. Treatment was for the most part symptomatic. He believes chemotherapy valueless and serum nearly so. No hospital cross infections occurred. The patients were confined in a special ward but not isolated from the rest of the hospital. No special measures were taken to prevent contact with other patients. He relied entirely on D.D.T. and ordinary cleanliness to prevent spread of the disease to other patients in the hospital.

Trench Fever: These cases were under the care of Dr. Mohr who knows of nothing but symptomatic treatment for the disease. The method of diagnosis will be discussed under the heading - Dr. Weyer.

Dr. Lippelt, Chief of the Bacteriology Department.

Dr. Lippelt was attached to the Afrika Korps during the war and says that he saw and treated about 150 cases of relapsing fever. He thinks the cases were louse-borne relapsing fever but since from his statements they were all sporadic cases, it seems more likely that they were tick-borne. He used only standard treatment (neoarsphenamine) and has no contribution of value to make.

Dr. Weyer, Entomologist.

Dr. Weyer is an able man but is badly handicapped by lack of space and facilities for investigation. He has brought the enodagnosis of trench fever to a fair degree of perfection. Trench fever, also called Wolhynian fever, is a chronic disease frequently lasting for two years or even longer, and is characterized by irregular attacks of a very irregular fever and pains over the long bones, especially the tibia. There is no headache, usually no loss of appetite, and the liver and spleen are not enlarged. The disease is found most commonly among those living under unfavorable conditions of hygiene and nutrition. Dr. Mohr believes that the disease is far commoner than is suspected, and that it is often diagnosed as a rheumatic condition. The only cases positively diagnosed in Germany recently were in soldiers returning from the Eastern front, particularly Russia and Poland, and a few cases from Greece and the Balkans. It appears to be

a wartime disease but both Dr. Mohr and Dr. Weyer think that further study will reveal its presence among civilians in peace time, living in a state of squalor. The only way of positively identifying the disease is by Xenodiagnosis carried out as follows: Lice reared in the laboratory for generations and fed daily on a suspected case for from five to seven days. The stools of the lice are examined daily for Rickettsia by staining a smear made from the stool with Giemsa stain. The presence of Rickettsia in the stools furnishes presumptive evidence only, since the species of Rickettsia cannot be identified with certainty from smears of stools. Seven days after the last feeding the lice are sectioned and the intestinal tract spread out on a slide. After fixation, the gut is stained with Giemsa; characteristic extracellular Rickettsia quintana provide a positive diagnosis. The method gives good results even during asymptomatic remissions of the disease. It was further checked by transmitting Trench Fever to patients with parasitism. Xenodiagnosis is considered to be entirely accurate when the result is positive. However, there is no negative check.

Dr. Vogel, Parasitologist.

Dr. Vogl is working on Schistosomiasis using Schistosoma japonicum. His technique is the same as that of Dr. Kikuth of Elberfeld (described in CIOS Report: Pharmaceuticals at I.G. Farbenindustrie Plant, Elberfeld, Germany. A Supplementary Report).

Professor Vogel is one of the foremost authorities in the world on the subject of Bilharziasis which he has studied intensively for 15 years. He has in the last few years been making an experimental study of acquired immunity to Schistosoma infection, and has found a method of producing it in monkeys by infecting the animals with parasites of one sex only. These produce immunity but, of course, cannot produce ova and, therefore, do not give rise to pathological effects.

Dr. W. Weise, Chief of the Department of Clinical Chemistry.

Dr. Weise has devised a method for atebrin determination in blood, urine and stools based on fluorometric analysis, which he claims is accurate to plus or minus 50 gamma in clinical atebrin prophylaxis. His findings are that no difference in blood levels exist when the drug is given daily or semi-weekly as long as the total amount remains constant. This is true

after two or three weeks of atebrin administration. Blood level is constant showing no peaks or valleys even on semi-weekly administration. Dr. Weise considers that from a scientific standpoint 0.06 gm. atabrin daily is no more efficient than 0.2 gm given on two non-successive days each week. However, from the military standpoint it is easier to administer atebrin daily than semi-weekly. Although not a clinician, Dr. Weise has never observed psychoses or other toxic effects from atebrin prophylaxis. He believes there is true atebrin elimination by bowel based on the following observations: When atebrin is administered orally, more of the drug is excreted in feces than in urine; when atebrin is administered intramuscularly about equal quantities are found in the urine and feces.

Dr. Weise has devised a nephelmetric method for the determination of sontochin in body fluids. Sontochin is more slowly eliminated by the body than quinine, but more rapidly eliminated than plasmochin. A transcript of this method was obtained from Dr. Weise and is attached (see Appendix I).

Professor Reichenow.

Professor Reichenow has recently worked particularly on the subject of the exo-erythrocytic phases in the life cycle of the malarial parasite - a subject with great practical implications since it is believed that these are the phases in which the parasites are inaccessible to schizonticides such as atebrin and quinine. He has been working with *p. praecox* and *p. cathemerium* infections in canaries. Early in the war, Professor Reichenow published the results of work begun in Tanganyika in 1937, on East African coast fever of cattle. He claims to have worked out the complete life history of the responsible parasite. Professor Reichenow is a protozoologist of great experience and competence, but of retiring personality.

4. Interview with Professor Dr. Horst Habs, Professor of Hygiene Medical Faculty, University of Hamburg, and chief of the Department of Hygiene of the City of Hamburg.

Professor Habs was interrogated in prison (Huttengefangnis, Hütten Str. 39-42) to which he had been committed for his Nazi activities. From June 1941 until September 1943 he was in Greece as consultant in Hygiene to the German forces. Since then he has been back in Hamburg. Dr. Habs was very anxious to be of assistance and freely answered questions and volunteered information

He was closely questioned regarding preventive measures in the Balkans.

Malaria was very prevalent in the German troops in Greece. Preventive measures consisted in: 1) personal protection - nets clothing, etc., 2) antilarval measures - Paris green, larvae-eating fish (Gambusia), drainage, and 3) 0.06 g. of atebrin daily, which Dr. Habs thought insufficient.

During the occupation of Greece Dr. Habs was in charge of the malaria control program for the Wehrmacht. He claims to have taken over and extended the work of the Rockefeller Foundation in Greece, relying to a great extent on public health officers of the Greek government trained by the Rockefeller Foundation. He conducted extensive surveys and found malaria most intense along the coast and in the large valleys, particularly the valley of the Struma. He considers A. elutus the chief vector.

His interest in Greece was confined to transmission of malaria and control of the mosquito vectors. He had nothing to do with treatment of the disease. Dr. Habs was not enthusiastic regarding airplane dusting with Paris green because it was uneconomical and the Germans were very short of Paris green. Best results were obtained by hand spraying swamp margins with Paris green and with oil. Spraying of D.D.T. on breeding places was tried on a small scale since 1943 and results were very good, but the Wehrmacht never had enough material for use on a large scale. D.D.T. was also used for spraying houses and barracks to kill imagoes. Dr. Habs considered this the best way to use D.D.T., especially if a power sprayer is available. "Anosal bombs" were apparently not used. The Wehrmacht apparently had no effective repellent, as Dr. Habs considered repellants useless. He was enthusiastic about the role of Gambusia in assisting to control Anophles breeding in Macedonia and in Southern Greece. He says that while Gambusia could never be relied upon for complete control, still control by other measures were enormously simplified. Dr. Habs stated that the Wehrmacht first used D.D.T. as a lousicide in Russia in 1942.

Dr. Habs also acted as advisor on drug prophylaxis. He used only atebrin and quinine, and considers them equally effective. Atebrin was used in doses of 0.06 gm. daily. He thinks that this is no more effective than some total weekly doses administered on two days of the week, but daily administration is easier to carry out in an army.

In areas in Greece where malaria was intense, practically all troops eventually acquired the disease in spite of prophylaxis. As a general rule atebrin administration was begun three days before troops moved into an endemic area.

For treatment of malaria the general routine in the German army was: 0.3 gm. atebriin daily for 7 days followed by plasmochin 0.02 gm daily for 3 days. Troops were then returned to duty. Dr. Habs believes that atebriin and plasmochin should not be given concurrently because of increased toxicity, although Professor Hauer of Berlin reports excellent results from combined use with no undue toxicity.

Dr. Habs believes that atebriin by mouth is nearly always adequate for vivax malaria but not for falciparum, as he thinks many cases refuse atebriin. He advises 0.03 to 0.06 gm daily for 2 or 3 days to be given intramuscularly. This is then followed by the usual oral treatment for 7 days. Dr. Habs advises also the same routine for cerebral malaria.

Kala azar: Dr. Habs saw only seven cases, all from Greece or Crete. He used Solustibosan concentrated, and thinks the drug is better tolerated than the old preparation, but there was too few cases and the follow-up was too poor to judge the effectiveness of the treatment. He has not used Stilbasmidine.

Bacillary Dysentery: was a great problem in Greece. Dr. Habs thinks vaccine is of doubtful value, but considers sulfadiazine treatment useful.

Amoebic Dysentery: Dr. Habs claims that he did not hear of many cases in the army. As far as he knows there is no improvement on the emetin and yatren treatment. He does not think that the German army used Gavano or the chlorine-substituted preparation similar to yatren.

Pappatacci Fever: Dr. Habs stated that spraying of bed nets with D.D.T. produces dramatic results in the prophylaxis of this disease. He knows of no treatment.

Water purification in the German army is chiefly by a form of portable pad filter, "Tornisterfiltergerat", made by the Seitz Co., Mannheim. Dr. Habs arranged for a demonstration of this filter at the Military Hospital, Langehorn. The filter weighs 20 kgm. and can be carried on a man's back. It will filter up to 200 liters per hour. It was distributed, through ordinance channels, to all filed troops of the German army in the scale of 2 per company (150 men).

It is suggested that filters of this type would be very valuable in S.E. Asia Command in solving the problem of the removal of amoebic cysts from water. There must be hundreds, if not thousands, of these filters in Germany which could be requisitioned. It would be very necessary to requisition also all available pads and to make arrangements for further manufacture of pads. A filter was requisitioned and sent to London.

At the Military Hospital stores a chemical agent for the purification of water - Microfur (Katedyn Co., Berlin) was noted. The Oberarzt and Oberfeldwebel said it was new, but they did not know its composition. It is not a chlorinating agent. A sample has been obtained.

Dr. Habs stated that the best German delousing agent was Lauseto (Bayer). A sample was obtained. Its effect in clothing was stated to last six months in spite of many washings provided the temperature was not raised above 50 C). The clothes are initially wrung out of a 1 per cent solution.

Dr. Habs said that the chief Consultant in Tropical Medicine for the German army was Professor Ernst Rodenwaldt, Professor of Hygiene at Heidelberg.

Dr. Habs did not think there had been any medical liaison between German and Japanese forces.

5. Air-raid Shelters.

There are three general types of air-raid shelters in Germany: 1) underground, 2) reinforced concrete structures built above ground, and 3) combination above and below-ground shelters.

1) Underground Shelters: One of these was visited in Hannover. It is located under the main railroad station. It consists of four very large rooms fitted only with beds and makeshift benches. The ventilating system was grossly inadequate, and the air was quite foul. It is presently being used to shelter German civilians who are living under most unsatisfactory conditions. The kitchen was a small room about twenty by twenty feet, and thick potato soup was prepared there, which was the only meal served. The sanitary arrangements were crude and inadequate.

2) Above ground Shelters: There are two types of these structures. The first is a small cylindrical reinforced concrete shelter with conical roofs. These shelters were small and equipped only with benches. They were intended for use only for an hour or two during raids, and are of no medical interest. The second type of above ground shelter is much more elaborate. One of these was visited in Hamburg. They were usually built in pairs -- one large one containing a hospital unit, and a smaller one containing rooms for shelter only. A pair of these shelters is located in Hamburg where the ground water level is too close to the surface

to permit underground shelters, and another identical pair is located in Harburg. The larger one visited in Hamburg required one year to build. It is roughly rectangular in shape, with cylindrical towers forming each corner. The dimensions are as follows: Height 48 meters; area 2700 square meters. They are five stories high. They are built of special high-compression reinforced concrete, and painted black. The dimensions of the floors are as follows: The roof is 4.2 meters thick, and the other floors are 2.8 meters thick. The sides are composed of two walls, the outer of which is two meters thick, while the inner is one meter thick. Around the top of the structure is a balcony composed of concrete about two meters thick. On this balcony there are located about ten 50 mm. anti-aircraft guns, and a larger number of 28 mm. guns. Above the balcony, on the roof, are four pairs of large anti-aircraft guns, each pair consisting of two guns of 128 mm. Immediately under the roof, and opening on the balcony, ammunition is stored. In the center of the roof is a radar plane-locating device, and around the balcony there are pictures of landmarks in Hamburg (church steeples, etc.), showing the exact distance of the landmark from the gun. This is obviously for purposes of triangulation. On the balcony is a large movable crane which handles gun barrels and heavy equipment. During the war, the material occupied the top floor of the structure. The other four floors were used for hospital and shelter purposes. The shelter rooms are about twenty by twelve feet, and furnished with benches. During raids, all of the people of a single neighborhood came to the same shelter. This was considered an important factor in keeping up civilian morale. The various rooms were connected by wide corridors, and the different floors by elevators and wide stairways. All outer doors were constructed of one-inch steel sealed with rubber, so as to be gas-proof. There are no windows, but slits with gas traps permitted the escape of air to the outside. Each floor had a special air-conditioning unit, with arrangements for temperature control, dehumidifying, and gas decontamination by means of activated charcoal. The air was distributed around the shelter by means of large overhead conduits. In the event that one or two of the units should be put out of commission, the remaining units were sufficient for ventilating the whole structure. The structure was illuminated by electricity, furnished by connection with the city system. An individual Diesel-operated electrical system was provided in the basement for emergency use. Water supply was from the city mains. Sewage was disposed of by pipe connection with the city sewage system. An individual water supply was available from wells under the structure, provided with an electric pumping

installation. Communication within the structure was by private telephone, which also had outside connections. Some idea of the effectiveness of this shelter is shown by the fact that it received nine direct bomb hits -- two hits slightly damaged the balcony, and other hits were on the roof and damaged the concrete to a distance of only about 50 mm. The structure was designed to accommodate 17,000 persons, but frequently as many as 23,000 were housed during raids. The people entered the shelter when the air-raid warning was received, and left as soon as the "all-clear" was given. As a rule they remained in the shelter only a matter of from one to three hours, and consequently no facilities for cooking food were required. Ample washrooms for men and for women, and separate toilets, were available. The hospital was located on the second floor, and occupied about one-third of its space. The hospital was administered by the Harbor Hospital of Hamburg, and was under the direct charge of Dr. Brütt, who was assisted by Dr. Schroer and another permanent physician. In addition to this permanent staff of three, two other physicians from the neighborhood attended during air-raids. Ten nurses comprised the permanent staff and forty others were assigned for duty during air-raids. The ten nurses and three physicians of the permanent staff all lived in the structure. The hospital had accommodations for 106 patients. Patients were cared for in small wards of from six to twelve beds. A special elevator brought wounded patients directly to the receiving room. The hospital had the most modern equipment seen in Germany. There were two aseptic operating rooms, and one septic operating room -- all equipped with shadowless lighting. The walls of the operating rooms and the corridors were painted with liminous phosphorus paint, for use in the event of lighting failure. The surgical instruments were the best obtainable. In addition to the three operating rooms, there was one cystoscopic room, completely equipped. There was an obstetrical delivery room, with complete obstetrical equipment. There were two dietary kitchens furnished with stainless steel tables, sinks, etc. The cooking equipment was all electrical. There was a permanent X-ray room with developing room attached. In addition, portable X-ray equipment was supplied, patients were kept in the hospital until they became ambulatory. Not only were emergencies cared for, but actual clinical research was conducted in this hospital. Important investigations on the use of the internal splint method for setting bone fractures -- first described by Professor Kuntscher -- were carried out. The hospital was in full operation when visited. Physicians were questioned regarding the effect of the absence of sunlight on convalescents, inasmuch as no sun-lamps were provided. Both Dr. Brütt and Dr. Schroer said they could notice no difference in the promptness of recovery caused by absence of sunlight.

3) Combination Above-and Underground Shelters: One of these shelters, operated by Städtisches Krankenhaus Notstadt on Haltenhoff Strasse No. 41. Hannover. was visited.

This is a reinforced concrete structure similar in general to the one described in Hamburg, but smaller and less elaborate. It had five stories, four of which were above ground, and one below ground. The dimensions were approximately twenty by forty-five meters. The roof is of reinforced concrete 3.25 meters in thickness, and the intervening floors 0.25 meters in thickness. The outer walls are 2.7 meters thick. The four stories above ground were used exclusively for shelter during air-raids. They are divided into rooms about twenty-five by ten meters, furnished only with benches. During air-raids this shelter housed 25,000 persons, who were forced to stand packed tightly together on the floor and on the benches to save space. No facilities for feeding were provided. Sewage disposal is by direct connection with the city sewage system. Water was provided from the city mains and by wells under the structure for emergencies. Electricity was supplied by the city, but this structure had accessory Diesel engines for emergencies. Only one ventilating system was provided, and it was obviously inadequate. The air was foul and was pumped through the conduits by noisy electric fans. Heating was provided by a coke-burning furnace on the basement floor. The hospital on the lowest floor below ground level accommodated one hundred patients in wards of twenty to thirty beds. There were two operating rooms and only portable X-ray equipment. There were two dietary kitchens and quarters for ten nurses and three physicians. This hospital was much less elaborately equipped than the one in Hamburg. It was built adjacent to the main hospital, and during raids as many patients as time and space permitted from the hospital were removed to the shelter.

There are about twenty-five shelters in Hannover -- four or five of which are underground.

6. Tierärztliche Hochschule, Hannover.

This school was found 75% destroyed. It is primarily a teaching institution for training doctors of veterinary medicine. It is the best equipped institution of its kind in Germany. In normal times it had twelve full professors each with three or four assistants in addition to laboratory technicians. The usual registration was about 600 students. The course required four years. The staff is as follows:-

Professor Dr. Fritz Schönberg, Animal Nutrition. He is an internationally-known authority on the subject, but was not

available in Hannover.

Professor Görtze, Internal Medicine. Not available.

Professor Schmidt, Parasitology. Killed in air-raid. Has not been replaced.

Professor Henkel, Director of the Institute and Professor of Surgery. No recent research of importance. He has used Klöntscher's internal splint on small animals. He says that it is unsuited for use in larger animals.

Professor Opperman, Internal Medicine. Available in Hannover

Professor Kuhrs, Anatomy. Available in Hannover.

Professor Frankwortt, Chemistry. Available in Hannover.

Professor Wagoner, Bacteriology. Available in Hannover.

Professor Trautmann, Physiology. Available in Hannover.

The school contains most modern equipment, including aseptic and antiseptic operating rooms, X-ray equipment for large and small animals, an excellent pathological museum and modern laboratories fully equipped for teaching. Because of disruption due to air bombardment there has been no important research done in the past few years. Although original investigations are a primary aim of the institution, when specific questions were asked regarding prevention and treatment of hog cholera, rabies, Bang's Disease and mastitis of cattle, no information was obtained.

7. Rijks Institut voor de Volksgezondheid, Utrecht.

Interview with Professor Dr. W. AEG. Timmerman (director) and Dr. N.W. van Esvald (Pharmacologist).

This institute is the central testing laboratory for the standardization of vaccines, sera, insulin and posterior pituitary extract. It also produces vaccines and sera of standard types for use in Holland. Limited production was carried on during the occupation. It is anticipated that when Penicillin production in Holland is feasible, the standardization of this material will also be undertaken.

At present production is totally suspended, through lack of fuel and containers (particularly 1 cc. ampules). It is

Dr. Timmerman's intention to come to England within a short time to discuss the rehabilitation of his institute. It would appear that nothing of any consequence has been carried out in this institute during the war.

8. Interview with Professor Dr. Kögl, Organic Chemistry Laboratory, Rijks University, Utrecht.

Professor Kögl has devoted his time during the war to work on egg-yolk biotin (called by Dr. Kögl, a-biotin), examination of carcinomatous tissues for D-glutamic acid and on auxins.

He has determined the structure of egg-yolk biotin which is less active than the biotin from liver and milk (called by Dr. Kogl b-biotin). Reference: Kögl and Berg "Über die Konstitution der Biotin", Zeitschrift für Physiol. Chem. 281, 65 (1944).

His work on D-glutamic acid in the hydrolysates of cancer tissue was discussed and it was learned that he has done considerable confirmatory work on his theory during the war. Dr. Kögl regards the presence of D-glutamic acid in cancer tissue as proved, and is anxious to take this up again with British and American workers. He has published an account of part of his work. Reference: Kögl, Erxleben und Veersen "Über die Bestimmung von D-Glutamin Säure in Tumorhydrolysaten mit Deuterium als Indicator", Zeitschrift für Physiologische Chemie 277, 251 (1943). Dr. Kögl claims that the failure of other workers to confirm his findings is due to differences of technique; his assistant Miss Erxleben had demonstrated the method in Dr. Hans Fischer's laboratory at Munich, and that subsequently they had been able to confirm his work.

9. Interview with Professor J. V. Koningsberger at the Botanische Laboratorium, Utrecht.

"Survey of the Research-Work on Antibiotic Substances in the Netherlands".

"In experiments on the infection of seedlings of grasses by various specimina of Pythium, A van Luijk found in 1932-1933 that Pythium de Baryanum is a rather strong parasite, when working in sterilized garden soil. When the soil had not been sterilized no parasitical

activity was stated. On the other hand the following phenomenon was observed. In the controls in non-sterilized soil the slightly older seedlings showed symptoms of a disease, apparently caused by a parasite, present in the non-sterilized soil. These symptoms, however, did not occur in the pots with sterilized soil, in which Pythium de Baryanum behaved as a parasite.

"Here the surprising result was obtained that a disease causing soil lost its infectivity by adding a parasite to it.

"At that time in the U.S.A. phytopathologists already had started to investigate similar phenomena, that were ascribed to some antagonistic action between various micro-organisms mutually. The production of toxic substances was thought to be the causal agent of this antagonism. Among the European phytopathologists generally these phenomena, as far as they had the interest, were due to the competition between the micro-organisms concerned in respect of essential factors as food, light, space, etc.

"The observation mentioned above led van Luijk to pay special attention to phenomena, indicating antagonistic actions in his further phytopathological experiments, first with grass-seedlings and later with lucerne. Soon special experiments were focussed on producing antagonism. Firstly externally sterilized seeds of grasses germinated in pure culture in culture tubes and then the seeds were infected, before or after their germination, with all possible combinations of 6 different species of Phycomycetes. These fungi had been isolated from the roots of diseased grass-seedlings.

"With these combinations results were obtained, varying from a 100 % inhibition of the germination to clear and pronounced stimulation of the growth. The latter phenomenon rather frequently occurred when using saprophytic fungi and combinations of them. In some cases the stimulation was very strong. Probably this must be due to the fact that several seeds hardly germinate in an entirely sterile medium. Saprophytic fungi and bacteria seem to attack the skin of the seed and thus promote the germination (effect on the permeability of the seed skin?).

"In several of these orientation experiments van Luijk incidentally isolated Dematioides (Pullularia) pullulans with a strong antagonistic activity against Pythium. That means "strong" for van Luijk's experience, that at that time still was deficient. The activity also is present in the filtrate (by means of a

SEITZ-filter) if it is not sterilized. After heating up to 100°C, the antagonistic activity had disappeared and was replaced by a notable stimulation. In dilutions of the non-sterilized filtrate an antagonism still was observable up to a dilution of 1 to 16.

"Dematiu pullulans therefore produces two substances with an opposite activity; a substance with antibiotic action against Pythium., that is thermolabile, and a thermostable substance that stimulates the growth substances. There was, however, thus far no opportunity to study this substance more profoundly.

"Up to this stage van Luijk mainly had worked with fungi and bacteria, isolated from diseased grass seedlings. Some of the micro-organisms as f.i. Dematiu were obtained by incidental infection of the cultures. The observations brought him to the hypothesis that the health of culture crops for a good deal must be ascribed to the presence of antibiotically active micro-organisms. If this hypothesis hold true, one can expect vigorously active fungi and bacteria to be present in soils, where the culture crops are healthy.

"Later on the same track of thought has been extended on the health of animals and men in the period that van Luijk worked in Utrecht. Resistance or tolerance against all kinds of parasites partly would be due to the presence of micro-organisms in the "portae" where they would produce strong antibiotics. According to this view a strong mutual effect would exist between the constitution and the antibiotic activity of the in- and external microflora. In the literature several indications may be found, which endorse this hypothesis. It will be discussed when reporting the later work at Utrecht.

"The earlier work in Baarn mainly was focussed on testing the hypothesis from a Phytopathological point of view. As many as possible various kinds of fungi and bacteria were isolated from spots where culture crops were growing well. The experiments on antibiotic activity partly were done by adding living fungi and bacteria to the tests. Later almost exclusively filtrates and sterilisates from the culture media, in which the micro-organisms had grown, were used. For large scale tests the method of SEITZ-filtration was too cumbrous. As soon as it was clear that often thermostable antibiotic substance are produced, the research almost exclusively has been pointed in that direction and the extracts of the media were freed from living macro-organisms by boiling. Recently, during the most difficult period of the work(since October 1944: no gas, no electricity, often no water), in Utrecht a method has been developed to test under non-sterile conditions. This makes the boiling or SEITZ-filtration superfluous and when searching the most efficient organisms no antibiotic substances ought to be destroyed by boiling.

"During the period in question good results were obtained with various micro-organisms. The most surprising one was got in a series of isolations from the air, garden soil and leaf-mole, in two of which a Penicillia had been isolated. It proved that in some cases the sterilized culture liquid, on which this Penicillia had been growing, still completely inhibited the growth of Pythium in dilutions up to 1 to 1280. The fungus proved to be Penicillium expansum. In the phytopathological literature already mention has been made of the antagonistic activity of this species against Sclerotinia fructicola.

"The major part of van Luijk's scarce spare time during his work in Baarn further was devoted up to the 1st of January 1940 to research on this Penicillium. One of the factors studied was the influence of the culture medium on the production of the antibiotic agent(s). It showed that the concentration and nature of the C-nutrition is the most important item next to the age of the culture. Antibiotic substances were only produced with mono- and disaccharides as a C-source; maltose and sucrose yielding the best results. Though the development of Penicillium expansum on polysaccharides rather was better than worse than on mono- and disaccharides, its antibiotic activity proved to be much less. It further was conspicuous that maltose gave good results, while those on malt extract were much poorer. The optimal concentration of the saccharids proved to be 3-4%.

"Asparagin as C-source yielded very poor results. Later it was found in Amsterdam that an addition of asparagin to a sucrose containing solution improved the production of antibiotic substances.

"In the first experiments maltose was much better than sucrose; in later tests, however, the results were rather variable. This probably must be due to the origin of the maltose.

"As for the age of the culture it was stated that the best results were obtained in cultures of 3-4 weeks.

"As far as time was available also some orientation experiments were done on the nature of the antibiotic agents. Heating of the culture liquid up to 115°C for one hour and to 110°C for half an hour proved to decrease the antibiotic effect against Pythium to activity. The antibiotics proved to be adsorbed by silica and Norit-coal. Since there was a great interest among van Luijk's co-workers at that time on the effect of pH upon the activity, also the pH was determined several times. In the weakest dilutions, still capable to inhibit the development of Pythium,

the pH proved to be about 5-6, at which Pythium uses to grow vigorously.

"It was known from the literature that in 1929 Fleming discovered a Penicillium with a strong antibiotic activity against several bacteria. Also he found, as a topscore, a complete growth inhibition in a dilution of 1:1280. It was clear from the beginning that the Penicillia of Fleming and of van Luijk were not identic; that of Fleming belongs to the group "chrysogenum" and was labelled as P. notatum. Although there are points in which the agents apparently are similar, there is one feature in which they diverge with certainty: according to Fleming the metabolic products of P. notatum have a basic reaction, whereas those of van Luijk's species are distinctly acid.

"During the last year of van Luijk's work in Baarn (1939), he stated that consistent morphological differences occur within the expansum group. These differences also occur in strains developing from one single conidium or from a short chain of 3-6 conidia. The main difference is the kind of mycelium formed: there are strains, which develop much air-mycelium, and others, that produce abundantly conidia. Typical differences in antibiotic activity of such strains do not occur, though at that time already it seemed that the abundant production conidia coincides with a high antibiotic activity. Later, in Utrecht, it proved that a rich white air-mycelium preludes on a certain deterioration of the culture in so far that the production of antibiotics decreases. When continuing the culture of such a strain the yield of antibiotics mostly within a short time sinks to zero.

"Several genera of fungi, mainly parasiting on plants, were tested on their sensitivity against the antibiotic agent of Penicillium expansum. Besides Pythium also species of Phytophthora, also belonging to the Phycomycetes, proved to be very sensitive. The same holds true for strains of Rhizoctonia and Thielavia, causing rot of roots and stems, and that are sensitive to high dilutions of the sterilized filtrate.

"On the other hand the species of Fusarium are very tolerant against the agent, as had already been mentioned in the literature. Also the species of Penicillium and Gliocladium and among the plant-parasites Coniothyrium Fuckelii and Physalospora Cydoniae are tolerant to a high degree. The last mentioned fungi have thickened cell walls and are strongly pigmented.

"Apart from the Phycomycetes Rhizoctonia and Thielavia also the fungi Fomes annosus, Armillaria Mellea, Merulius domesticus, Verticillium alboatrum and Cladosporium fulvum are very sensitive.

The sensitivity of *Merulius domesticus* perhaps could give occasion to experiments to combat this fungus, that often causes great damage to houses, by means of concentrated preparations of the antibiotic substances.

"At that time in Holland the literature reporting on the toxic effect of Fleming's penicillin on various pathogenic bacteria and the application of it for medical purposes still was unknown. On his own hook van Luijk accounted for the possibility that in this direction something could be attained with the antibiotic agent of *Penicillium expansum*. To that purpose it was tested whether the skin fungus *Trichophyton rosaceum* was sensitive to the *expansum*-agent: it proved to be very sensitive. 5 drops of culture liquid in 10 cm³ of fresh culture medium entirely inhibited the development of *Trychophyton*.

"The passage on this experiment in a short paper in the "Vakblad voor Biologen" (Professional paper for biologists) in 1939 has been the direct motive for the research on behalf of the pharmaceutical firm Brocades, Stheeman and Pharmacia after van Luijk's retiring.

"Numerous specimina of fungi were found to be able to act antagonistically upon *Pythium*. During the experiments in Baarn, however, no one of them could compete in activity with *Penicillium expansum*. Several *Penicillia*, however, have a stronger activity against *Fusarium* than *Penicillium expansum* or are about of the same degree of activity.

"With peptone as a N-source *Fusarium* itself developed an antagonistic activity, whilst this substance had an adverse effect on the production of antibiotics by *Penicillium*.

"A bacterium (*Bacillus vulgaris*?) was isolated from leaf-mold, that had a much stronger antibiotic effect against *Fusarium* than *Penicillium*. Against *Pythium*, however, the bacterial agent was much less active than that of *Penicillium expansum*. In pure culture this bacterium quickly lost its ability to produce antibiotics. This feature is, after van Luijk's experience, generally still more pronounced with bacteria than with *Penicillium*.

"*Penicillium expansum* and the bacterium were cultivated apart and combined and the activity of the culture liquid was tested on *Pythium* and on *Fusarium*. The combined effect against *Pythium* proved to be stronger than that of *Penicillium expansum* alone, that had the strongest effect of the two, when applied apart.

"As at best the effect of the culture liquid of Penicillium expansum equalled the toxicity of a 0,2% solution of sublimate, so that of the bacterial culture liquid did against Fusarium.

"Of all Penicillium-species tested at that time Penicillium Claviforme was the most active when cultivated on filter paper as only C-source. In that case it still produced antibiotic substances that were rather active against Pythium.

"In the end of 1939 van Luijk retired as a phytopathologist of the "Willie Commelin Scholten" Institute at Baarn (Director: Professor Dr. Joh. Westerdijk) and got his pension. On the initiative of Dr. J. J. Duyveme de Wit, leader of the research department of Brocades, Steseman and Pharmacia, van Luijk was enabled to continue his work on this chapter in the Botanical Laboratory of the State-University, Utrecht (Director: Professor Dr. V.J. Koningsberger) and got a grant from that firm. The work in Utrecht can be divided in four stages and started on the 1st of January 1940.

"The first problem to be solved was how to get a quantity of culture liquid, on which Penicillium expansum had grown, sufficient for experiments on a semi-technical scale and adequately to purify the agent for clinical experiments. Fortunately the full time of van Luijk from now on was available for this work and the scope of the laboratory in Utrecht was more adequate to this purpose than that of the Institute at Baarn.

"As has been mentioned it had already been stated that the activity of the agent is kept when evaporating the culture liquid to a large extent. Moreover it had been found that at a subsequent treatment of the concentrated agent by means of 95% aethanol a precipitate is formed and that by far the major part of the agent remains in the liquid. After repeated washings with alcohol (aethanol), practically no agent is left in the precipitate. It now was stated that a further purification could be attained by shaking that concentrated solution with ether after removing the aethanol. It further was tried to purify the preparations by absorbing the agent to Norit-coal, that had already proved to be an adequate absorbent. After studying the most suitable amounts of coal and temperature van Luijk succeeded in absorbing all the antibiotic substance, active against Pythium, to Norit-coal. It proved to be difficult, however, to eluate the agent from the coal, that apparently absorbs it strongly. Several times fairly good results were obtained, but often these could not be reproduced.

Later similar variable results were reported from the Amsterdam-branch (Director: Professor Dr. C. B. Jansen), where only recently a method that yields consistently good results, has been developed.

"Since 1943 as much culture liquid (on which P. expansum had been growing) was produced as possible. To this purpose an electrically heated, air-conditioned room was used for the cultivation of the fungus in about 500 large Erlenmeyer-flasks. Every three weeks the culture liquid was filtered and then stored in large containers.

"The second phase began with experiments on cattle (of the veterinary faculty by the kind aid of Professor Beyers). Especially skin diseases, caused by fungi, externally were treated with the concentrated and purified agent. In several cases the results were striking and very promising.

"In 1942 Miss Dr. Jaarsveld in Amsterdam resumed this line of research and tested the effect of the agent on bacteria pathogenic to men. She also did experiments on animals to study the effect of the partly purified agent upon the skin by external application. In pure cultures of several pathogenic bacteria very good results were obtained with the concentrated preparations of the first work in Utrecht. In the application on the human or animal skin, however, irritating by-effects occurred.

"A further purification of the solutions was reached by shaking the ether treated solution with chloroform. Efforts to purify the chloroform soluble part by absorption to Norit coal failed since the elution of the coal was inconsistent here too. After the treatment with chloroform a concentrated preparation was obtained that, in the adequate dilutions proved to be as effective against pure culture of bacteria as the ether extract without causing undesired by-effects when applied to the skin. It proved impossible, however, to get a still higher degree of purity with the scope of the Botanical Laboratory. For that reason the aid of Professor Dr. Jansen (Amsterdam) was called in, whose co-workers Dr. Luyten and Oosterhuis did the further chemical work.

"So more time got free to concentrate the research in Utrecht on the cultivation of the fungus and to isolate new vigorous strains of Penicillium expansum. The latter work became necessary since the earlier isolated good strains gradually became deteriorated and stopped to produce antibiotics in commercial quantities.

"Originally new strains were isolated by digging in sliced of apple in the soil on spots, where *Penicillium expansum* could be expected. After a week a high percentage of these slices proved to be covered with *Penicillium* that could be isolated. Later this method was simplified by putting a small sample of soil in a Petri dish and placing a slice of apple next to it. This method had the advantage that soil samples for this purpose could be sent in from different parts of Holland. Often the fungus developed *coramia* on the apple and it then was very simple to transfer a single coremium into a flask with culture liquid and to get the strain directly in a pure state. It proved to be desirable to add a small quantity of culture liquid, in which a good strain had been growing; of course, this liquid had been filtered by SEITZ-filtration or sterilized beforehand.

"When this method of obtaining large series of new strains had been developed and much time had to be spent to the testing of these strains on their production of antibiotics, a special assistant J. Wybrans, was appointed and charged with this work. Mr. van Luijk, moreover tried to isolate micro-organisms producing antibiotic substances in quite a different way. It has already been mentioned that van Luijk had drawn up the hypothesis that the resistance of men against certain diseases possibly would be due to the presence of such micro-organisms in the main "portae" of infections, that is in the first place to oral cavity. This hypothesis is endorsed by well-known facts. So f.i. it is known that saliva acts as a strong antiseptic against several micro-organisms. According to a certain German school the mucous membrane would produce these antiseptic substances, but other people believe that they are produced by micro-organisms. *

* Later van Luijk amplified his hypothesis to the entire intestinal canal, the respiratory organs and the skin. It is mentioned in the literature that from the birth *Staphylococcus epidermidis* is present in the human skin. It seems probably that here a kind of symbiosis occurs and that the resistance against certain skin-and wood parasites is due to antibiotic substances, produced by this *Staphylococcus*. Possibly a healthy constitution is favorable to the development of this bacterium and to its production of antibiotic substances. On the other hand it does seem likely that the same bacterium grows a parasite on men with an unhealthy constitution or that other pathogenic bacteria in such a case get a chance to predominate. Van Luijk also suggests that antibiotic substances are produced by the micro-flora of the intestines and the feces and that these substances can spread in the body in the same way as hormones. Possibly this accounts for the resistance against and the susceptibility for certain diseases/

"The advantage of getting antibiotic substances from such oral micro-organisms, isolated from the mucilage of healthy persons, is that one may expect them to be free from any toxic by-effects, and that such micro-organisms will not produce toxic substances, in adequate culture media either.

"Much time has been spent to the isolation of oral micro-organisms and among these van Luijk found a *Candida* strain that developed a notable antibiotic effect against *Pythium*. In dilutions of 1 to 100 after five days the growth of *Pythium* was checked by the culture liquid on which *Candida* had grown. Measures taken to isolate also micro-organisms from selected healthy and diseased people from a tuberculosis health result were hampered by the circumstances of the war.

"In the meantime much time was devoted to the isolation of more strains of Penicillium expansum, and yet another assistant E. Samuels Brusse and two analysts were appointed for the enlargement of this work and for the production of starting-material of antibiotic substances on a semi-commercial scale.

"All this work was in full swing, when, beginning in August 1944, it gradually became impossible to continue it. In the first place the assistants had to "submerge", then the gas supply was stopped, a few weeks later that of electricity followed, and finally there was no heating in the laboratory and even for longer periods, no water. It therefore became impossible even to sterilize glasswork and culture media, to run air-conditioned rooms or even thermostats, etc. Also methylated spirit and matches were very scarce and so, when inoculating a culture tube, one had to discriminate, whether he would keep the spirit burning or save spirit and spend another match between two inoculations! No one can imagine the primitive conditions under which has been worked during the last eight months of the war.

"Still some work could be done.

"It can be expected that numerous micro-organisms develop at a low temperature during the autumn and winter on decaying and rotting plant material, on and in the soil, and that there will be a

(continued from Page 61 *) As long as this hypothesis is not endorsed by more facts it seems advisable not to advertise it, since medical scientists probably will receive it with a certain scepticism. The results of more experiments with the yeast-like fungus Candida must be waited for.

strong competition between them. Van Luijk thought it possible that a number of these micro-organisms would produce antibiotic substances in their "struggle for life". Since they develop in nature at low temperature it seemed probably that they also would produce these substances, when cultivated at low temperature. So hundreds of new isolations were made during this period to be tested on their antibiotic activity. Several decades of them deserve a further investigation. Among them are several new strains of Penicillium expansum.

"Further test methods had to be developed which could be applied under the described adverse circumstances. Here only those methods that proved to be useful to a certain extent are described briefly.

"A very simple Pythium-test has been developed as follows: In a test tube 10 cm³ of tap water (not sterilized) is added to a small quantity of culture liquid on which the organism to be tested has been growing. Then a small slice (standardized: 6 to 9 mm; 1 mm thick) of agar (solidified KNOP's solution with 2½% of sucrose) is added, on which Pythium has been inoculated. These slices are taken from a culture plate inoculated with this fungus, that under the prevailing conditions (no sterilization) normally only can be cultivated on an acid medium to avoid the predominance of bacteria. The small amount of nutrients, present in the agar slice and diffusing in the water, still is sufficient to get a fairly strong growth of Pythium in the liquid. In this highly diluted medium, however, micro-organisms from outside practically do not develop, so that the test is not obscured by contaminations. The test tubes therefore were even not protected with cotton wool, that was very scarce too. According to van Luijk the relative sterility of the test might be due to antibiotic substances, produced by Pythium itself.

"This method, that saves much time and material, certainly is also useful in normal times. By applying this method the number of tests can be made threefold at least with the same scope. It seems desirable to try to adapt this method for testing pathogenic micro-organisms too.

"Another promising test method, born of our emergency, is based on the diffusion rate of the antibiotic agent(s). In a Petri-dish a solution of 1.5% of plain agar is poured, that after solidification gives an agar layer of exactly 2 mm thickness. At

one side a segment is removed and replaced by a segment of exactly the same size, taken from another Petri-dish, in which the organism to be tested has grown on a normal KNOP's agar with sucrose. In van Luijk's experiments this organism was Penicillium claviforme in a large number of strains.

"The culture from which the segment is taken may be young or old, but in the case of dusting fungi the culture should not be too aged. Perpendicularly on the borderline between the inserted segment and the plain agar small agar slices (of the same size as mentioned in the former test) with KNOP's solution and 2.5% of sucrose, inoculated with Pythium mammillatum, are placed on certain distances (1 - 2 cm) apart. Since the plane agar is not a suitable substrate for Pythium (for contaminations neither !) this fungus will only spread as far as it can grow on the intake of nutrients from the KNOP-sucrose agar slice and on that part of the agar plate in which the nutrients diffuse from these small agar slices. In the meantime nutrients and also antibiotic substances will diffuse from the inserted segment. The area covered by Pythium after a few days gives clear information on the content on the antibiotic substances, diffusing from the inserted segment.

"It may be mentioned that this method has several promising features for the future. The rate of diffusion largely depends on the size of the molecules of the diffusing substance. According to Fick's law one can calculate the molecular weight from the rate of the diffusion of an unknown substance. In the case of antibiotic substances we probably have to deal with several agents. Possibly the described test method can replace the chromatographical method as used to separate mixtures of substances according to their molecular weight. The biological "indicator" quantities of substances concerned than the chromatographical method with - perhaps - uncolored substances.

"Further the same principle of diffusion might be useful for the purification and isolation of the separate agents from a mixture, for the separation of colloidal agents, etc. Since thus far it has been impossible to do exact experiments a further description of possible applications of the diffusion principle may be taken for granted. It is hoped that further research along these lines soon can be resumed.

"Finally, it may be mentioned that van Luijk also resumed earlier work (of the Baarn period) with Penicillium calviforme.

It appeared from the literature that from this fungus an antibiotic substance has been isolated that in a pure crystalline state got the name claviformin. According to the Amsterdam research team this claviformin probably is identical to one of the agents of Penicillium expansum, that also has been obtained in a pure state. If it might turn out that P. expansum does not produce more important agents than P. claviforme does, the latter has several advantages as a producer of antibiotic substances over P. expansum.

"In the first place P. claviforme does deteriorate in pure culture; the strain used by van Luijk has been kept in pure culture for over 20 years (in the collection of the Central Bureau of Fungi Cultures, Baarn). With P. claviforme much work and time could be saved, since P. expansum must be continuously isolated in order to have available sufficient active strains.

"Further P. expansum strongly dusts: its spores spread throughout the laboratory and easily cause contaminations. With the coremium-forming P. claviforme this danger is much less.

"Finally, as has already been mentioned, P. claviforme grows well and produces antibiotic agents as well on plain filter paper (it grows on wood in natural state) and therefore easily can be cultivated in pure culture by untrained people.

"An elaborate program has been developed for the continuation of the work for the next future. Thus far all the research has been paid by Brocades, Stheeman and Pharmacia. For that reason van Luijk as well as the author do not freely dispose of the results and the possible application for pharmacognostic purposes. On the other hand it would be greatly appreciated when the Dutch research could be linked up with that in Britain and the U.S.A., where it certainly is far ahead and already has yielded the most remarkable results".

Utrecht, 6th June 1945.

(Summarized and translated from
comments of Mr. A. van Luijk)

(Professor Dr. V. J. Koningsberger)

10. Laboratory of Physiological Chemistry, Netherlands
Institute of Nutrition, Amsterdam.

Dr. B. C. P. Jansen, Director of the laboratory and Dr. J. J. Duijveme de Wit, who is directing the combined work of the Utrecht-Amsterdam groups on antibiotics, were interviewed. These investigators re-stated briefly the work which was reported to us in Utrecht by Dr. Koningsberger.

Expansin (Patulin?) is very active against certain molds. It has been used clinically against fungus diseases of the skin (athlete's foot), and found to be very effective. For this work it was made up in an ointment base containing 5 mg. Expansin per cc.

The crude broth from *Penicillium expansum* has been found to be active against tubercle bacilli *in vitro*. The filtrates, after removal of expansin, were observed to be active against *Staph. aureus* and to have an anti-urease activity. Crystalline expansin has been tested clinically against lupus, but the results have been contradictory. Expansin was found to be inactive against certain viruses. This group claims to have isolated an antibiotic active yeast from the human oral cavity.

11. Medical Faculty of the University of Utrecht.

Professor Dr. C. D. der Langer, Professor of Medicine, stated that medical research has been practically at a standstill during the five years of the German occupation. This was confirmed in interviews extending over two days and no data of value were obtained.

Professor der Langer (age 56) has had 21 years experience in the tropics (Dutch E. Indies) and is very anxious to form a team of Dutch medical men of good tropical experience to go out and staff a hospital, (in Ceylon for preference), which might be used for training doctors of the Netherlands forces in Tropical Medicine. He is a man of considerable ability and the author of a standard work on Tropical Medicine.

12. Institute of Tropical Medicine, Leiden.

An interview with Professor B. C. Flu, Director of the Institute and Professor of Tropical Medicine and Bacteriology, elicited the following information. The war has stopped work on tropical medicine in Holland. No research has been done. The medical problems of the Dutch E. Indies were discussed. The chief diseases are malaria, dysentery (bacillary and amoebic), typhoid, and scrub typhus. In Sumatra dengue is very common, and leptospirosis occurs.

The prevention of amoebic dysentery among the Netherlands forces in the Dutch E. Indies used to be achieved by a rigid order that tea must be drunk and never water. It was an offence for a soldier to be found with water in his water bottle instead of tea. The order was easy to enforce because the troops preferred tea. This simple practical measure is of great importance because contamination of streams with amoebic cysts is universal owing to the native habit of defaecating into streams. An invasion force drinking even apparently clear water is likely to have very heavy casualties from amoebiasis. It must be remembered that chlorination does not destroy all amoebic cysts. In the opinion of the investigators this simple and time-proven device should be brought to the notice of the American and British medical departments of the fighting forces.

13. Medical Faculty, University of Leiden.

Professor Kuenen, Professor of Medicine was interviewed, but no data of importance were obtained.

14. Institute of Tropical Medicine, Amsterdam.

Professor Dr. Swellengrebel, Acting Director and Dr. van Steenis were interviewed at length. No research work was done during the war and no data of importance were obtained.

15. Medical Faculty, University of Amsterdam.

Professor J. J. van Loghem, Rector of the University and Professor Formijne, Professor of Internal Medicine were interviewed.

Both confirmed the general standstill in medical progress in Holland imposed by war conditions. No data of importance were obtained.

III. PHARMACEUTICAL TARGETS IN NORTHERN GERMANY AND HOLLAND.

L. P. Beierdorf & Co, A.G., Hamburg.

Persons interviewed were: Dr. Alfred Simon, Technical Director and Carl Claussen, Commercial Director.

This company owns and operated three plants in Hamburg. The plants locations and products manufactured at each establishment are as follows:-

Plant No.I Hamburg 30, Eidelstedterweg 48
Main office.

Manufactures adhesive plasters, medicinal plasters, medicinal and pharmaceutical preparations, soaps and cardboard boxes for finishing.

Plant No.II Hamburg-Billbrook, Berzeliusstrasse 35.

Manufactures war materials for ointments and other medicinal preparations.

Plant No.III Hamburg-Lokstedt, Mathilden Strasse 12.

Manufactures toothpastes, tubes, tin boxes and cardboard boxes for finishing (facilities destroyed).

The adhesives made during the war were produced from Buan and a polyethylene product imported from Italy. Paper and cellulose acetate fabric were coated with adhesive to form the plasters. The firm is well equipped for the manufacture of plasters.

Among the many pharmaceutical products manufactured by this company Eucerinum anhydricum, Scabron and Pandigal appear to merit

consideration.

The Berzelius Strasse plant was found to be in good operating condition and moderately well equipped.

Real estate and number of buildings:-

Plant No.1.	10,299.9	sq m.	13	buildings
Plant No.2.	14,980.2	"	6	buildings
Plant No.3.	23,364.0	"	2	sheds
Dwellings	8,251.4	"	5	buildings
Land under cultivation for food supply	57,325.0	"	4	barracks

Total real estate: 114,520.5 square meters.

Present conditions of the buildings:-

Plant No. 1	2 buildings destroyed; 3 partly destroyed; 3 buildings repaired; 3 partly repaired; 2 buildings are to be repaired.
Plant No. 2	Slightly damaged.
Plant No. 3.	2 buildings, porter's lodge, store sheds and barracks, partly destroyed. 3 buildings and one barrack partly restored.

Foundation of Firm. October 1, 1882.

Capital and its Development up to This Date.

On 1 June 1922	M 11.000.000
On 25 November 1924	rm 3.300.000 (transposed to Reichsmark)
On 17 December 1928	rm 5.000.000 (increase of capital)
On 28 November 1941	rm 15.000.000 (capital adjustment)

Names of Directors of Scientific Staff.

Original Directors. Dr. Oscar Tropowitz from 1882-1918 deceased
Dr. Otto Hanns Mankiewicz from 1910-1918 deceased
Mrs. Oscar Tropowitz from 1918-1920 deceased

Directors since 1922 Dr. Willy Jacobsohn
Christoph Behrens
Thaddaeus Smielowski deceased
Dr. Hans Gradenwitz deceased
Dr. Eugen Unna
Max Ohm deceased
Dr. Alfred Simon
Carl Claussen

Scientific Staff Dr. Alfred Simon
Dr. Walter Mauss
Dr. Paul Mohs
Franz Schneider
Dr. Ruhkopf

Dr. Wilke)
Dr. Kirchner) Not yet returned from military
Dr. Fendius) service.

Total Number of Employees and Factory Workers.

	<u>31 July 1939</u>	<u>30 June 1943</u>	<u>31 May 1945.</u>
Employees (salaried)	409	296	217
Factory Workers	1575	1166	482
	<u>1984</u>	<u>1462</u>	<u>699</u>

List of Products.

Medicinal Plasters:

Leukoplast: Fabrics or special paper coated with adhesive mass, corresponding to the Collempastrum zincii DAB 6.

Hansaplast:	Rapid wound dressing, made from Leukoplast as underlayer, with an impregnated muslin cushion.
Special plasters:	Self adhesive plasters containing various substances with pharmacological effects which are used against rheumatism, boils and carbuncles, corns, etc. Trade names: ABS-Plaster, Capsiplast, Elastofurun, Elastocorn
Pandigal :	Galenical preparation of the pure glycosides from digitalis lanata in form of drops, tablets and suppositories.
Tussipect :	Galenical preparation of the crystallized ammonium salt of saponins from primula elatior (alatior acid) in form of syrup, drops, dragees and prescription mixtures.
Scabron :	Remedy against scabies, fat free, with sulphur and p-oxybenzoic acid esters as the effective ingredients.
Temagin :	An analgesic, a combination of caffeine, phenacetin, bromdiethylacetylurea and tetramethylen-phenyl-methylpyrazolon according to DRP 668,628.
Eucerinum anhydricum :	An ointment base consisting of mineral fats and purified fractions of the wool fat alcohols. (water in oil emulsion).

Monthly and Yearly Production of Main Products.

In 1938

Monthly average 1938

Pharmaceuticals:

Eucerin	36 000 kilos	3 000 kilos
Foot-ointment	72 000 boxes	6 000 boxes
Pandigal-preparations	52 000 kilos	1 088 kilos
Temagin	1 800 kilos	160 kilos
Tussipect-preparations	54 000 kilos	4 500 kilos
Baby Cream	24 000 boxes	2 000 boxes

Adhesive Plasters, Dressings and Medicinal Plasters.

1 300 000 sq m. 100 - 110 000 sq m.

Composition of Leading Products.

Adhesive Plasters: The plaster mass contains according to the purpose it is to serve -
25 - 35% rubber or rubber substitutes
15 - 25% resins
15 - 25% softener
15 - 30% filler material

Pandigal : 1 tablet, 1 g. solution, 1 suppository each contains 0.4 mg of the pure glycoside mixture.

Tussipect

Syrup	:	About 50% cane-sugar-solution with 0.15% Ephedrin, 0.03% saponin salt and aroma-substances.
Drops	:	Aqueous solution with 1% Ephedrin, 0.4% saponin salt and aroma-substances.
Dragees	:	Coated sugar-tablets with 0.66% saponin salt.
Scabron	:	10% sulphur and 1% oxybenzoic acid-benzyl-ester in emulsion-form.
Eucerin	:	Melting of vaseline with alcoholic fractions from 18% wool fat.

Manufacturing Processes.

1. The Ammonium Salts of Primulae Saponins.

Raw material required for processing 1000 kg. root:-

10000 kg	Radix primulae
7 kg	Alcoholic ammonia
70 kg	Ether
320 kg	Hydrochloric acid
400 kg	Ammonia (d - 0.91)
50 kg	Active carbon
830 kg	Methyl alcohol

Process of Manufacture:

100 kg of the macerated root are stirred with 600 kg water and 5 kg ammonia solution (d-0.91) for 24 hours at room temperature. The juice is pressed off and the extraction repeated. The combined pressed juice is heated to 80-90°C and the raw saponin precipitated with an excess of hydrochloric acid. Excess acid is largely removed by repeated washing with water and centrifuging. To the saponin residue add sufficient alcohol so that the final concentration of alcohol is about 70%. Add animal charcoal (about 5% of the dry substance) and reflux for several hours. Filter and evaporate under reduced pressure until granular saponin begins to separate. Filter on a suction filter until fairly dry, then dissolve in 5 parts of methanol. If necessary decolorize again with animal carbon and to the clarified solution add an excess of alcoholic ammonia. Upon heating, the crystalline ammonium salt precipitates. Yield about 80% of the crude saponin.

2. Manufacturing Process for Eucerin.

Raw material required for processing - 100 kg Woolfat.

100 kg	Woolfat
10 kg	Alcohol 96%
20 kg	Benzine (extraction benzine)
22 kg	Potassium hydroxide (50% solution)
11 kg	Sulfuric acid
21 kg	Active carbon

Process of Manufacture:

100 kg woolfat are saponified with 23 kg potassium hydroxide (50%) and 450 kg alcohol (70%) by boiling 5 hours with stirring. The solution in the saponification vessel is extracted with 500 liters benzine (naphta), then 6 times with 150 liter portions benzine. The combined benzine extracts containing the wool fat alcohols filtered and clarified by the addition of 2 kg active carbon. The benzine solution is washed 4 times with 100 liters quantities of alcohol (70%) and the benzine removed by evaporation followed by steam distillation.

The alcoholic solution is acidified with sulfuric acid to decompose the soaps and the alcohol removed by distillation.

Yield 40-50% wool fat alcohols

50% wool fat acids

For the manufacture of Eucerin, 6 parts of wool fat alcohol are melted with 94 parts vaseline.

3. Manufacture of 3,4-cyclotetramethylene-1-phenyl-2-methyl-5-pyrazolon.

To 100 kg of 3,4-cyclotetramethylene-1-phenyl-5-pyrazolon (Annalen El7, 102(1901) dissolved in 300 kg potassium hydroxide (20%) slowly, add with stirring, 80 kg dimethylsulfate. The resulting methylated product is then dissolved in benzol, shaken thoroughly with aqueous potassium hydroxide and the benzol removed by distillation. The residue is then distilled twice under vacuum and permitted to crystallize. The 3,4-cyclotetramethylene-1-phenyl-2-methyl-5-pyrazolon forms colorless needles having a melting point of 106-107°C, and is soluble in water (1:70) and readily soluble in alcohol, acetone and benzol.

4. Manufacturing Process for Seabron.

Raw material for 100 kg.

28 kg	Potassium hydroxide (50%)
11.5 kg	Sulfur
8 kg	Bentonite
10 kg	Sulfuric acid
1.2 kg	Cetylalcohol
0.8 kg	Cetiol
2.5 kg	Sapo kalinus
1 kg	Nipabenzyl

Process of Manufacture:

Dissolve 64 kg sulfur in 150 kg potassium hydroxide (50%) and dilute with water to 500 liters. Then add 800 kg Bentonite suspension (6%) and precipitate the sulfur by stirring with dilute hydrochloric or sulfuric acid (caution: hydrogen sulfide is evolved.) Wash the resulting suspension until free of acid and filter until the sulfur oil contains 12% of sulfur. A soap emulsion is prepared by heating the soap kalinus, in water and slowly adding with stirring the melted cetyl alcohol, cetiol and nipabenzyl. Allow the mixture to cool and add to the sulfur-bentonite suspension.

5. Manufacturing Process for Digitalisglycoside Mixture (Lanadigin).

Raw material for 1 kg Lanadigin:-

2000 kg	Alcohol 96%
450 kg	Chloriform
25 kg	Lead acetate
25 kg	Litharge
7.5 kg	Ammonia
7.5 kg	Ammonium sulfate
1500 kg	Digitalis lanata leaves.

Process of Manufacture:

100 kg coarsely powdered Digitalis-Lanata leaves are extracted, with slow stirring, for several days with 300 liters 96% alcohol and the extract collected. The pressed juice is mixed with an equal volume of water to which is then added 3 liters of lead acetate solution and the mixture adjusted to the neutral point with ammonia. The precipitated lead is filtered off and the clear filtrate extracted with 50 liters of chloroform. The chloroform is distilled off under vacuum. The residue is taken up in diluted alcohol and a second lead precipitation is carried out. The filtrate, light yellow in color, is extracted with chloroform yielding three layers. The lower layer contains substances readily soluble in chloroform, while the upper layer contains those substances easily soluble in diluted alcohol. The emulsified middle layer is carefully separated and dried under vacuum. The residue is dissolved in 70% alcohol, and on slow evaporation crystals of the glycoside mixture separate.

Working Formulas for Leading Pharmaceutical Products.

Pandigal-tablets: raw material for 100 kg.

Mixture of digitalis glycoside	0.4 kg
Milk sugar	95. kg

additional substances for tablet-making -

Gelatine	0.12 kg
Stearic acid	0.5 kg
Alcohol	2 kg
Wheat Starch	4.5 kg
Talcum	1 kg

Pandigal drops: raw material for 100 kg

Mixture of digitalis glycoside	0.04	kg
Glycerogen	5	"
Glycerine	10	"
Alcohol	20	"
Aqua dest.	65	"

Temagin: raw material for 100 kg

Coffeine	4	kg
Phenacetini	40	"
Bromdiath.acetyl.ureu	16	"
3,4-cyclotetramethylene-1-phenyl-)	24	"
2-methyl-5-pyrogalton)		
Potato starch	10	"
Sodium chloride	4.8	"
Magnesium sulfate	0.8	"
Sweetening substance	0.64	"
Aethylvanillin	0.06	"
Oil of peppermint	0.11	"

Auxilliary substances for making tablets:

Gelatine	0.4	kg
Stearic acid	0.48	"
Alcohol	1.32	"

Tussipect: raw material for 100 kg

Syrup -

Sugar	52	kg
Formic acid	0.05	"
Benzoic acid	0.2	"
Ephedrin hydrochloride	0.15	"
Ammon. salt of primula saponin	0.031	"
Ammonia 0.91	0.25	"
Extr. thymi fluid	5	"
Water.	42.319	"

Drops: raw material for 100 kg

Ammon salt of primula saponin	0.4	kg
Ephedrin hydrochloride	1	"
Lamepon	1	"
Succus liquiritiae	2	"
Sweeting substance	0.02	"
Ammoniac 0.91	0.2	"
Couleur of sugar	0.75	"
Aromatic substances	0.08	"
Water	94.55	"

Baby-cream: Raw material for 100 kg

Eucerinum ahydricum	35	kg
Lanettewax	0.4	"
Vaseline	24.6	"
Zingoxide	2.5	"
Talcum	2.5	"
Benzoic acid	0.2	"
Glycerogen	1	"
Aqua dest.	33.8	"

Research Activities.

The research laboratories and technical library of this company were totally destroyed in July of 1943, consequently no research has been carried on in the intervening months. Prior to this time some investigations were initiated with respect to analysis, vitamins, disinfectants and remedies effective against scabies. Some work was also done on the use of suitable substitutes for natural rubber in the manufacture of adhesives. We received the distinct impression that very little in the way of original research has been carried out by the small scientific staff of this company.

The following publications have appeared since 1939:

Hans Ruhkopf: - Zur Kenntniss des Cyclotetramethylenpyrazolons (II. Mitteilung), Berichte der deutschen chemischen Gesellschaft 72, 1978, 1939.

Hans Ruhkopf: - Über einige Dioxo - pyrazolidine, Berichte der deutschen chemischen Gesellschaft 73, 820, 1949.

Hans Ruhkopf: - Über die Druckhydrolyse substituierter Barbitursäure, Berichte der deutschen chemischen Gesellschaft 73, 938, 1940.

Hans Ruhkopf: - Zur Kenntnis des Cyclotetramethylenpyrazolons Molekülverbindungen (III. Mitteilung), Berichte der deutschen chemischen Gesellschaft 73, 1066, 1940.

Effective Patents Held by This Company.

1. D.R.P. 535,675 Process for the manufacture of a wound dressing.
2. D.R.P. 427,274 and 514,096 Process for the manufacture of a digitalis glycoside.
3. Patent applied for - Sunburn preventive
4. D.R.P. 496,446 Process for the manufacture of a cough remedy containing Primulae saponin.
5. D.R.P. 668,628 Process for the manufacture of Temagin.

2. Chemische Fabrik Promonta G.m.b.H., Hamburg

The investigating team interviewed Herr Fritz Wiegand, plant manager and export director; Dr. E. Kamenz, technical director, and Herr Ph. Bitter, purchasing director, who were very cooperative in answering questions put to them and in supplying detailed information regarding business and other operations of the company.

This company manufactures and distributes a fairly complete line of pharmaceutical products derived from animal organs, glands and tissues. As examples may be cited extracts of the liver, adrenal cortex, posterior pituitary and stomach; thyroid extracts; a liver extract for the treatment of angina, thyroid extract; testicular hormone; heparin; as well as a number of standard pharmaceutical preparations containing such substances as iron, copper, and strychnine in organic or inorganic combinations.

It was our impression that the manufacturing and finishing processes were lacking in adequate control to assure the uniformity and potency of the products. The only laboratory available or intact was one small room in a converted shed, the staff consisting of one pharmaceutical chemist and an assistant. It is doubtful if any of the products distributed by this firm are characterized by proven therapeutic merit.

Chemische Fabrik Promonta was founded in February 25, 1919, with a capital of 100.000 Rm; in 1941 the capital was increased to 1.995.00 Rm. The firm employs 108 persons as executives and clinical assistants and 160 factory workers. At the present time the company is grossly over-staffed, which is a rather serious situation because working capital is being reduced at an alarming rate.

Organization of the Firm.

General Manager and Superintendant: Herr Herbert Giebel

Business Manager : . Dr. Max Oldach

Assistant Superintendant: Herr Fritz Wiegand

Scientific Staff: Dr. med. E. Haupt, at present with the police force, Hamburg.
Dr. med. A. Jores, pharmacologist, - absent
Dr. med. J. Wadel, pharmacologist, protective police, Hamburg
Dr. med. E. Wille, on leave of absence
Dr. H. Wolter, biologist, - absent
Dr. A. Selge, librarian
Dr. A. Detzel, chemist - absent
Dr. L. Klemm, chemist
Dr. A. Lang, chemist
Dr. L. W. Masch, chemist
K. Heidenhain, chemist
Dr. F. W. Kersandt, Berlin - absent.

Commercial Executives:

Purchasing	:	Philipp Bitter
Sales	:	Joh. Oliberg
Stock and Book-keeping	:	Philipp Bitter
Traffic Manager	:	Rudolf Timm
Banking	:	Heinrich Hansen
Legal	:	Dr. jur. Warner Poelchau

Manufacturing Organization:

Director	:	Dr. Erich Kamenz
Technical Laboratory, in charge of	:	Dr. Lang
Pharmacology Laboratory	:	Dr. med. A. Jores
Ampul Department	:	Dr. L. Klemm
Tabletting and Coating	:	Arthur Brecht, pharmacist
Vacuum Drying and Extraction	:	Max Blumenhagen

Adhesives:

Engineer Hugo Hindemann

Library (destroyed) and Records:

Dr. A. Selge.

The company also operated an adhesive plaster division located in Schenefeld, Kreis.

Pinneburg.

During the period of interrogation, Herr Wiegand stated that the records of the firm, including manufacturing processes, etc., were deposited at Garmisch-Partenkirchen, Maximilianstr., 19, c/o Jebel.

Real Estate and Building

The plant on the Hammerlandstrasse occupied about 11.000 sq m. of land, but 900 sq m. are not in use. It consisted of 25 buildings of which 10 were totally destroyed and 15 are still usable because they have either been repaired or were not hit. The number of intact buildings does not truly represent the present manufacturing potential, as the premises were hit repeatedly in air raids and much equipment was destroyed. Some reconstruction work has been attempted, but at best it is a temporary measure.

List of Products and Manufacturing Formulae.

A complete list of the products manufactured by Promonta as well as detailed manufacturing formulae submitted by the firms are included in the following tabulation.

Asthmatrin

Papaver. hydrochl.	0.545	%
Novocaine "	0.070	%
Acet. Chloroform	0.363	%
Sodium chloride solution	97.500	%
Physormon N 2 VE	1.350	%
Adrenaline (Ciba)	0.0545	%
Hydrochloric acid	0.011	%
Sodium sulfite	0.001	%
<hr/>		
	100.0	%
<hr/>		

Sterilization: Solution boiled for 10 minutes before the addition of Adrenaline and Physormon

Packaged: 3 Ampuls of 1 ccm.
10 " " 1 ccm.

Sales, 1942: 204.- ltr.

Campiol

Freezing point - 3 to 4°C.

Pyrethrum-blossoms extract	3.00	kg) concentrated to
Lecithin ex ovo	0.750	") 150 according
Alcohol	ad	100.000 ltr) to instructions
Distilled water		300.000 ltr)
 Glycerine	50.000	kg	
Texapon, recrys.	3.000	"	
Sugar	250.000	"	
Sodium benzoate	3.000	"	
Agar-agar	6.000	"	
Tap water	100.000	"	
Orange essence	2.000	"	
Orange juice	80.000	"	
Citras oil	1.000	"	
	1000.000	ltr.	

Cholotonon p.i.

Gall and liver extract (especially prepared)	20.0	%
Tricresol	0.4	%
Distilled water	ad	100

Sterilization: Filtration through EK filter

Package : 3 Ampules of 1 ccm.
10 " " 1 ccm.

Citropepsin:

	%	1 Tablet
Pepsin 1 : 10000	0.200	0.001 g
Citric acid	50.000	0.250 g
Amylum tritici	39.300	0.197 g
Talcum	10.000	0.050 g
Gelatine powder	0.500	0.002 g
	100.000 %	0.500 g

Packages of tablets : 20
100
240

Sales 1942: 2674.- kg

Cortidyn p.i.

Adrenal cortex extract (specially prepared)	Corresponding to 5 mg. gland per cc.
Benzoic acid	
Nipasol	0.01 %
Distilled water	0.10 %
ad	100 %

Sterilization : Filtration three EK-filter.

Package : 3 Ampules of 1 cc
10 " " 1 cc.

Cutren

Novacaine hydrochloride	1.000	%
Thiourea	10.000	%
Urea	89.000	%
	100.000	%

Eutonon-Drops

100 g - 7.5 g. dried liver substance

Aqueous liver extract	52.500	%
Sisi F	21.200	%
Undiluted syrup	17.250	%
Alcohol	7.100	%
Sodium Benzoate solution	1.500	%
Citric acid)	0.450	%
Caramel)		
	100.000	%

Eutonon

Ampules of 1 cc.

Dried liver extract (specially prepared)	7.5	%	
Dextrose	2.5	%	
Benzoic acid	0.1	%	
Distilled water	ad	100	%

pH: 6.5

Sterilization: 2 X 30 minutes at 100 with an interval of 48 hours.

Feometten

Ferrum reductum 4.62 %

Talcum 4.15 %

Z M Fe:

Sugar	44.39	
Milk	9.61	
Ferr. reduct	<u>4.61</u>	58.61 %

M Kb Fe:

Milk	10.39	
Cocoabutter	1.73	
Amylum solani	1.73	
Ferr. reduct	<u>4.53</u>	15.38 %

Z. Va.:

Sugar	0.77	
Vanillin	<u>0.08</u>	0.85 %

Thy m. M.:

Thyroid	0.138	
Milk	<u>0.015</u>	0.15 %

Cinnamic acid 0.39 %

Cugl-Preparation:

Cal.glyc.phosphor	0.020	
Copper sulfate	<u>0.020</u>	0.04 %

Dried skinned milk 15.81 %

100.000 %

Ferro 60 - Pastilles

Ferrocitrate	35.95 %
Ascorbic acid	0.45 %
Sugar	5.44 %
Powdered milk	2.92 %
Stearin	0.45 %
Sodium biphosphate	0.18 %
Powdered cocoa	4.04 %
Talcum	4.64 %
Dragee mass	45.92 %

100.00 %

Ferro 66 for Injections

Ampules of 5 cc

Ferrous glutamate	1.20 %
Dextrose	2.00 %
Ferrous ascorbate	0.23 %
Distilled water	ad 100 %

Sterilization: 2 X 30 minutes at 100° with an interval of 48 hours.

Iron content: 10 mg Fe per Ampule

Ferro 66 - Drops

Ferrous chloride, dried	11.840 %
Distilled water	27.720 %
Citric acid	3.020 %
Ferrum reductum	0.045 %
Gewürz-Lösung : Citrus oil 0.015	
Alcohol <u>0.075</u>	0.090 %
Glucose	49.750 %
Mixture with ascorbic acid: Citric acid 1.220	
Ascorbic acid 0.241	
Aqua dist. <u>6.080</u>	<u>7.540 %</u>
	100.000 %

Ferronovin liquid

100 0 - 134,5 kg.

Ferrous chloride	0.400 kg
Citric acid	0.400 "
Organ extract	2.765 "
Water	17.640 "
Sodium benzoate	0.300 "
Orange essence	0.260 "
Gewürzessenz	0.040 "
Cocoa distillate	0.280 "
Vanillin solution 18 %	0.240 "
Citrusol	0.170 "
Kapillärsirup	100.000 "
Glycerine	10.000 "
Color, chocolate brown	0.005 "
Alcohol 96 %	2.000 "
	134.500 kg

6.2.45. C3

Ferronovin - Powder

<u>LP:</u>	Press Juice of 22 kg fresh liver	2.000%
	Stomach, fat, dried	3.860%
	Dried skim milk	39.118%
	Wheat flour	1.200%
	Grain flour	4.800%
	Potassium biphosphate solution 10 %	0.022%
	Lecithin	<u>1.000%</u>
		52.000 %
	Testes purified	0.800 %
	Lecithin	4.000 %
	Calc.glyc.phosph.	2.510 %
	Siderac	1.070 %
	Powdered cinnamon	1.000 %
	Sodium chloride	0.300 %
	Potassium carbonate	0.500 %
	Powdered cocoa	2.500 %
	Aromatics	1.000 %
	Orange peel	1.000 %
	<u>Sugar/Vanillin:</u>	
	Sugar	1.00 kg
	<u>Vanillin</u>	<u>0.10 kg</u>
		1.100 %
	Sugar	21.700 %
	Milk	5.730 %
	Amylum solani	4.462 %
	Vitamin D-concentrate 20 cc.	0.018 %
	Magnesium carbonate	0.330 %
		<u>100.020 %</u>

27.3.44. G8

Hepatopson for Injections

Liver extract (specially prepared)
Tricresol
Saccharine
Distilled water

1 cc corresponds to 5 gm fresh liver

pH: 6.2

Sterilization: Filtration three EK-filter

23.4.45. G5

Hepatopson, forte

Liver extract (specially prepared)
Tricresol
Saccharine
Distilled water

1 cc corresponds to 10 gm fresh liver

pH: 6.2

Sterilization: Filtration three EK-filter

23.4.45. G5

Hepatopson - liquid

Working Directions -

50.72 kg Liquid liver extract - 12.8 kg dried extract, mix with
0.99 " Sodium-benzoate solution, 30 %
6.40 " 94 % Alcohol
0.04 " Hipasol dissolve, add to the extract
0.27 " Spice mixture :- 0.232 kg Orange essence
0. 36 " Spice extract and mix with
0.21 " 3.92 % copper sulfate solution

Then add:

41.37 % Dextrose, stir for $\frac{1}{2}$ hour

Bring to pH 5.6 with citric acid solution
Color

100.00 "

The mixture is allowed to stand for 14 days,
then filtered, and finally filtered through
a No. 5 Seitz filter.

20.9. 43.

Inkretan

Thyroid (0.44% iodine content, specially prepared)	4.50 %
Anterior pituitary lobe (100 ME)	0.800 %
Caramel	18.700 %
Dried skim milk	24.000 %
Sugar	6.000 %
Dragee mass	46.000 %

100.000 %

31.3.44. G8

Jodgorgon

Sugar	50.000 %
Powdered cocoa	40.000 %
Diiodotyrosine	10.000 %
	100.000 %

Neurosmon - strong

Cubes of 4.2 g.

Preparation "N"

Cerebrum	6.27 %
Spinal cord	4.39 %
Testes	2.00 %
Dried skim milk	12.55 %
Wheat germ	5.00 %
Lecithin	2.02 %
Sodium benzoate	0.31 %
Potassium biphosphate	0.05 %
Dried skim milk	12.65 %
	45.240 %

Caramel	18.750 %
Dried skim milk	7.010 %
Powdered cocoa	3.600 %
Cinnamon	0.650 %
Calc.glyc.phosph.	2.230 %
Ferrous oxide, saccharated	1.190 %
Magnesium carbonate	0.300 %
Strychnine nitrate	0.011 %
Sweetening	0.019 %
Vanillin	0.090 %
Sugar	13.180 %
Protigold	2.970 %
Sulfur D ₃	4.760 %

Neurosmon - weak

Cubes of 4.2 g.

Preparation "N"

Cerebrum	6.27 %
Spinal cord	4.39 %
Testes	2.00 %
Dried skim milk	25.30 %
Wheat germ	5.00 %
Lecithin	2.02 %
Sodium benzoate	0.21 %
Potassium biphosphate	<u>0.05 %</u>
	45.240 %
Caramel	18.750 %
Powdered cocoa	2.230 %
Cinnamon	0.650 %
Ferrous oxide saccharated	1.190 %
Magnesium carbonate	0.300 %
Sugar	14.550 %
Vanillin	0.090 %
Dried skim milk	11.800 %
Protigold	3.970 %
Calc.glyc.phosph.	<u>2.230 %</u>
	100.000 %

Go" 2.4.43.

Orsulon - tablets

	%	1 Tablet
Orsulon-calcium	72.710 %	0.352 g
Amylum tritici	14.740 %	0.066 "
Talcum	11.550 %	0.052 "
100.000 %		0.450 g

Orsulon - Suppositories

1 Suppository - 2.5 g.

For Adults:

Suppositol	58.33 kg
Orsulon-calcium	41.67 "
	100.000 kg

For Children:

1 Suppository - 1.1 g.

Suppositol	70.800 kg
Orsulon-calcium	29.200 "
	100.000 kg

Ocenta

Preparation "P"

Placenta, fresh 25 kg - dried	3.950 kg
Dried skim milk	44.625 "
Grain flour	4.500 "
Sodium benzoate 30 %	0.300 "
Lecithin	1.800 "
Potassium biphosphate 10 %	0.025 "
Powdered sugar	7.500 "
Protigold	<u>7.000</u> "
	69.600 kg
Ferrous oxide saccharated	2.900 "
Calcium glyc. phosphate	2.200 "
Dried skim milk	1.300 "
Orange peel	4.000 "
Sugar	19.930 "
Siderac	0.070 "
	100.000 kg

Philonin - salve

Vaseline, yellow	48.500 %
Wheat starch	18.000 %
Zinc oxide	18.000 %
Paraffin oil	10.300 %
Surfen	0.045 %
Trypaflavin	0.010 %
Silver nitrate	0.070 %
Water	1.600 %
Isopropylalcohol	3.000 %
Boric acid	0.670 %
Tumenol-ammon.	0.670 %
Copper oxquinoline sulfate	0.070 %
Balsam Peru	0.670 %
Chloretone	1.000 %
Cholesterin	0.250 %
	100.000 %

Physormon

Ampules of 1 cc

Posterior pituitary extract
(specially prepared)

Corresponds to 0.25 % Posterior
Pituitary Powder

Benzoic acid
Nipasol
Distilled water

Ca 0.03 %
0.10 %
0.01 %
ad 100 %

pH: about 5.0

Sterilization: Filtration through EK-filter

Praephyson - ampules

Ampules of 1 cc

Anterior pituitary extract
(specially prepared)

Corresponds to 7.5 % Anterior
Pituitary Powder

Tricresol
Distilled water

Ca 0.5 %
0.4 %
ad 100 %

Sterilization: Filtration through EK-filter

Profundol - tablets

1 Tablet

Bromidethylacetylcarbamidcitrate
Allyl-sec.butyl-barbituric acid
Stearin
Amylum tritici
Talcum

0.175 g
0.075 "
0.010 "
0.050 "
0.050 "

0.360 g

Promonta - Powder

PKT:

Stomach, dried, not defatted	0.64%
Brain, fresh - 24.-kg	5.48%
Wheat germ	5.48%
Protigold	4.80%
Sugar	2.56%
Sodium benzoate 93 kg	0.20%
Potassium bisphosphate	0.04%
Lag. 0.55 kg	<u>19.20%</u>

Milk Lecithin:

Dried skim milk	18.30%
Lecithin	<u>1.00%</u>

Wheat germ	5.00%
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Protigold	16.30%
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Dried skim milk	5.37%
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Sugar	26.20%
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Sugar Vanillin:

Sugar	1.20%
Vanillin	<u>0.12%</u>

Cugl-Preparation	0.04%
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Orange peel oil	1.10%
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E.P.:

Protigold	2.22%
Iron chloride	<u>0.45%</u>

Vitamin B₁ - Mixture:

Thiamin hydrochloride	0.004%
Sugar	<u>0.196%</u>

Calc.glyc.phosphate	2.50%
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Coriander	0.30%
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Egg Yolk	0.50%
	<u>100.00%</u>

Pro Ossa

Pro IV:

Sugar	21.00 kg
Milk	11.50 "
Lecithin	5.00 "
Stomach, dried, fat	3.50 "
Protigold	6.00 "
10% Potassium biphosphate solution	0.011"
	<u>47.011 kg</u>

Roasted Product:

Sugar	7.70 kg
Milk	3.25 "
Malt extract	0.58 "
	<u>11.500 kg</u>

E.P.:

Iron chloride	0.400 kg
Protigold	<u>2.20 "</u>

Sodium chloride

0.900 "

Calcium phosphate

14.000 "

Sugar

8.900 "

Cal.glyc.phosph.

0.020 "

Dried skim milk

5.000 "

Protigold

9.169 "

Jansen-concentrate 0.020 I

Spices I:

Aromatics. Orange peel	0.240
Coriander	0.068
Cinnamon	0.315
Dried skim milk	<u>0.277</u>
	<u>0.900 kg</u>
	<u>100.000 :-</u>

9.9.44 GO

Provitina - oil

100 l Provitina-oil consists of:-

Tuna fish oil, the content of Vitamin D corresponds to about	33.330 kg
Wheat germ oil	9.200 kg
Soya bean oil	33.300 "
Liver oil	16.170 "
	92.000 kg

Purginol

	<u>Strong</u>	<u>Weak</u>
Aloes	34.09%	17.05%
Extr. frangulæ	4.54%	4.54%
Sulf. precip.	1.13%	1.13%
Sodium sulfate	5.70%	5.70%
Fel Suis	4.54%	4.54%
Talcum	3.40%	3.40%
Milk sugar	---	17.04%
Dragee mass	40.90%	40.90%
	100.00%	100.00%

Rheumitren - liquid

Aqua dist.	54.00	kg
Triaethanolamine	5.00	"
Salicylic acid	8.00	"
Isopropylalcohol	23.20	"
Salicylaldehyde	0.50	"
Chloroform	4.50	"
Mitigal	0.20	"
Benzoic Acid	3.00	"
Yatren acid	0.20	"
Eutonon (1.0 kg dried)	1.40	"

100.00 kg

Rheumitren - salve

Water	35.72%
Potassium carbonate	1.68%
Glycerine	0.51%
Stearin	6.12%
Oil of Rosemary, French	2.75%
Lanolin	32.65%
Vaseline	10.20%
Mustard oil	0.51%
Fennel oil	5.10%
Oxyquinoline	0.50%
Sulfur oil	0.36%
Chloroform	1.02%
Iodine	0.10%

102.33%

Loss 2.33%

100.00%

Sanostol -fluid

Agar agar	0.30 kg
Sodium benzoate	0.25 "
Water	24.87 "
Sugar	55.12 "
Malt extract	12.00 "
Orange juice (Califora orange)	5.00 "
Citric acid solution	1.00 (0.18 kg Acid citric)
Curacao liquor	0.04 "
Vitamin oil-emulsion	1.42 "
	100.00 "

Sestron - Suppositories

Suppositol	74.470 kg
Potato starch	21.280 "
Sestron-Base	4.250 "
	100.00 kg

Sestron

Ampules of 1 cc

Bisphenylpropylethylamine	4.00 g
Hydrothloric acid 25%	2.40 g
Distilled water	ad 100 g

Sterilization: 2 X 30 minutes at 100° with
air interval of 48 hours.

Séstron - Longetten

	%	1 Longette
Sestron-Citrate (specially prepared)	27.900	0.140 g
Sacch. lact.	221.900	0.109 "
Amyl. trit.	5.970	0.030 "
Gelatine	0.260	0.001 "
Talcum	5.970	0.030 "
 Nucleus	62.000	0.310 g
Dragee mass	38.000	0.190 "
 1 Longette	100.000	0.500 g

Symbion - tablets

	1 Tablet	%
Ascorbic acid	0.025	0.31
<u>Vitamin B. mixture:</u>		
Sugar 0.551		
Vit.B.0.011	0.045	0.56
Sodium biphosphate	0.200	2.50
Powdæred cocoa	0.800	10.00
Sugar	0.625	7.81
Amyl. solani	0.028	0.34
Dextrose	4.671	58.40
Talcum	0.380	4.75
<u>Milk-coca Butter:</u>		
Dried milk 5.250		
Cocoa butter 1.750	0.560	7.00
Malt Extract	0.125	1.56
Milk	0.541	6.77
	8.0 g	100.00 %

Solvitren

Ampules of 5 cc

Sheep blood or Ox blood (specially prepared as described)	50.00%
Oxyquinoline sulfate	0.25%
Sodium sulfate	0.90%
Distilled water	ad 100%

Stomopson - granular

Stomach defatted	76.51%
Meat broth, powder	5.00%
Celery pulp, powder	6.43%
Celery top, powder	1.06%
Amyl. solani	11.00%
<hr/>	
	100.00%
<hr/>	

Testifortan - ampules

Ampules of 2 cc

Extract (specially prepared)	1.2 %
Yohimbin hydrochloride	0.057%
Papaverin. hydrochloride	0.050%
Nipagin	0.01 %
Benzoic acid	0.1 %
Distilled water	ad 100 %

pH: 4.0

Sterilization: 2 X 30 minutes at 100° with
a 48 hour interval

Vetren for Injection

Heparin (specially prepared) 0.100%
Distilled water ad 100.00%

Sterilization: 2 X 30 minutes at 100° with
a 48 hour interval

Viteminte

Vitamin E-concentrate	1.89%
Sugar	37.32%
Bolus alba	11.50%
Gelatine	2.23%
Talcum	5.66%
Amylum tritici	5.66%
Dragee mass	37.74%

100.00%

1942 SALES OF PRODUCTS

Asthmatriin-Amp	204.-ltr
Campiol	30478,- "
Cholotonon - strong	1447,-kg
Cholotonon - weak	1199.-"
Cholotonon p.i.	61.-ltr
Citropepsin	2674.-kg
Cortidyn-Amp.	81.-ltr
Cutren	1173.-kg
Eutonon-Amp	40.-ltr
Eutonon-liquid	1478.- "
Feometten	7412.-kg
Arsen-Feometten	6462.- "
Ferro 66 - drops	2046.-ltr
Ferro 66 dragees	1845.-kg
Ferro 66 p.i.	448.-ktr
Ferronovin	3271.-kg
Ferronovin - liquid	20618.-ltr

Hepatopson liquid	243.-ltr
Hepatopson Amp.	1135.-ltr
Inkretan	2456.-kg
Jodgorgon	53.-kg
Neurosmon - strong	3610.-kg
Neurosmon - weak	3390.-kg
Orsulon - tablets	370.-kg
Orsulon - cones	475.-kg
Ocenta	21762.-kg
Philonin - salve	10477.-kg
Philonin - suppositories	1103.-kg
Physormon normal	24.-ltr
Physormon forte	17.-ltr
Physormon Schnupfpulver	7.5 kg
Praephyslon-Amp.	190.-ltr
Praephyslon - tablets	230.-kg
Praelacton - cones	44.-kg
Profundol	307.-kg
Promonta	110210.-kg
Promonta with Arsen	12587.-kg
Provitina oil	57.-ltr
Pro Osen	13421.-kg
Purginol normal	391.-kg
Purginol fortified	768.-kg
Rheumitren liquid	2221.-ltr
Rheumitren salve	974.-kg
Sanostol liquid	380176.-kg
Sanostol-Longetten	2292.-kg
Sestron-Amp.	16.-ltr
Sestron - suppositories	141.-kg
Sestron-Longetten	80.-kg
Solvitren siccum	5862.-kg
Solvitren-Amp.	198.-kg
Symbion	14493.-kg
Stomopson	1516.-kg
Testifortan-Amp.	205.-ltr
Testifortan tablets	1272.-kg
Thalassan	6.-kg
Thio-Vetren	1.-ltr
Vetren-Amp.	236.-ltr
Vitemonta	1833.-kg

STOCK OF INTERMEDIATES AND RAW MATERIALS

on June 1, 1945

Preparation	Intermediates for	Raw Material for
a) <u>Organotherapy</u>		
Asthmatrip	3.000 Amp.	57.000 Amp.
Asthma Remedy		
Citropepsin	---	300 kg
Gastric ferment preparation		
Hepatopson Forte (Hepatopson pro inj.)	10.000 Amp. 20.000 Amp.	35.000 Amp., 25.000 Amp.
Antianemic from liver		
Promonta	5.000 kg	55.000 kg
Nerve nourishment		
Pro Ossa	1.000 kg	29.000 kg
Calcium vitamin preparation		
Cholotonon	---	2.400 kg
Organ preparation from the total liver-biliary tracts		
Ferronovin	---	10.000 kg
Liquid liver iron preparation		
Ocenta	---	20.000 kg
To increase lactation		
Stomopson	---	10.000 kg
Antianemic from stomach substance		
Vetren	100.000 Amp.	200.000 Amp.
Anticoagulant		

Preparation

Intermediates for Raw Material for

b) Hormone Preparations

Cortidyn - Standardized adrenal cortex extract	5.000 Amp.	25.000 Amp.
Inkretan - Hormonal Remedy	---	8.000 kg
Praephysen - Standardized anterior pituitary extract	30.000 Amp.	70.000 Amp.

c) Vitamin Preparations

Sanostol - Natural concentrate from livers of halibut and other sea fishes, citrus fruits and malt	1.000 kg	99.000 kg
Symbion - B-C vitamin product with glucose and phosphate	200 kg	9.800 kg

d) Iron Preparations

Feometten - Iron with copper	200 kg	1.000 kg
Ferro 66 - liquid	300 kg	2.100 kg
Ferro 66 - tablets, biologically active iron, stabilized by the reducing power of Vitamin C.	---	400 kg

e) Powder

Eukutol-Kinderpuder - Baby powder	300 kg	30.000 kg
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Research Program of the Scientific Staff of Promonta
During the Past Six Years.

The research program of Promonta was seriously curtailed as early as 1939, as a direct consequence of the war. Two of three physicians serving on the staff were drafted by the Wehrmacht in 1939 and the third man was taken later. Also many of their outside consultants were not available due to other commitments in clinics and hospitals. In general, it may be concluded that the research staff of Promonta was sales-minded rather than scientific. It was obviously their duty to produce profits rather than pharmaceuticals of merit having a sound clinical background. A cursory examination of the research activities reported by the firm for years 1939-1945 revealed no developments of substantial importance.

Acinormal

This is a complex sodium magnesium aluminium silicate which exerts an optimal buffering action in the acid range of hyperacidic gastric juice. The acid neutralizing power is claimed to be exceptionally high so that small quantities of the preparation produce a significant reduction in the high acid values in the stomach, without danger of alkalizing the gastric juices. Since Acinormal is insoluble in acid juices and does not yield soluble substances, there is no inhibition of the action of digestive ferments.

Campiol

Campiol is a biologically standardized extract derived from Pyrethrum flowers. In cold blooded animals it produces a lethal effect by acting as a muscle poison, while in warm blooded animals only intravenous administration produces death by direct effect on the central nervous system. This observation led to the development of Campiol, which has proved to be free from toxic effects and well tolerated in the treatment of Oxyuriasis.

Corticlyn

The problem associated with the preparation of the adrenal cortical hormone has been studied intensively for some years by the research division of Promonta, and their investigations led to the

preparation of Cortidyn. Since oral administration appeared to yield a satisfactory response Cortidyn drops were introduced in addition to the ampule which had been marketed previously.

Praesphyson Forte.

By the proper concentration of extracts of the anterior pituitary lobe, a highly active product containing 75 M.E. units of luteinizing hormone per cc. was developed.

Praelactin.

As derived from the anterior pituitary residue (see Process Section) it contains 400 pigeon units ¹rolacton per cone. The problem of producing a satisfactory and highly active lactation hormone preparation has not been approached from every angle. Other investigations are therefore necessary to obtain final information.

Provitina-Oil

Promonta's fish liver oil is claimed to be of high potency, containing 12,000 I.U. Vitamin D₃ and 12,000 I.U. Vitamin A per cc.

Vetren.

Pure heparin tested for its anticoagulant activity by means of animal and human blood; mainly used in connection with blood transfusions. One 2 cc. ampule inhibits the coagulation of 150 cc. of human blood for 2 hours.

Processes for the Preparation of Glandular and Organ Extracts.

Hipatopson (liver extract plus iron)

Extract 500 kg of fresh liver with 450 liters tap water for 1 hour at 28-30°C with constant stirring. Heat to 60-70°C and press out. Wash with 80 liters of water at 80°C. Evaporate

the 530 liters of solution to 20-30 % of the weight of the liver. The vacuum pan should not be filled to more than 1/3 its capacity because of foaming. The 130 liters of solution are transferred to a 400 liter stoneware crock and 25 kg ferrous sulfate (dissolved in water) added with vigorous stirring. The next day add 20 kg Ca O with stirring, then centrifuge. Wash the residue with 120 l. warm water and combine the washings with the main extract. The solution (Ca. 250 l.) is adjusted to pH 5.3-5.5 with 50 % H_3PO_4 (7-15 liters). By no means go below pH 5.1. Use Bromcresol Blue paper as an indicator.

Centrifuge and wash the residue with 50 l. warm water, combine the extract and wash fluid, then evaporate in vacuo to 50 l. Keep in a cool place overnight and centrifuge, wash the residue with 25 l. warm water, combine the extracts; heat the solution (Ca 75 l.) on the water bath to 40°C and add sufficient (4-5 l.) of 30 % Na OH to obtain a pH of 7.8-9.0. Use Bromthymol Blue paper as an indicator.

Filter off a small sample and add trisodium phosphate solution; if it becomes turbid, this proves that in acidifying too little H_3PO_4 has been used. In this case, phosphate solution must be added until a filtered sample remains clear upon the addition of phosphate. Centrifuge, wash the residue with 60 l. warm water, combine the liquids and centrifuge (Ca. 135 l.). Lightly acidify with citric acid and evaporate in vacuo to exactly 60 kg. Determine the dry residue.

Hepatopson - strong and for injections.

The extract obtained as above after the removal of excess H_3PO_4 , is used. Adjust the pH with HCl to 6.0-6.4 and dialyze in cellophane against 5 vols. water for 3 hours at 25°C. (Cellophane tube 10 cm diam.) Evaporate in vacuo until 1 cc corresponds to 5 g. fresh liver. (For "strong" 1 cc - 10 g. liver). This extract must meet the following requirements:-

- 1) The dry residue should be between 9-12 %; for the "forte" between 20-25 % (i.e. gms/100 cc).
- 2) The extract should not contain protein (negative sulfosalicylic acid test).
- 3) Should not contain more than 30 mg per cent Ca.,
- 4) Not more than 20 cc histamine as determined pharmacologically with the guinea pig gut.

5) The extract must be tolerated by animals (absence of temperature rise, pain, inflammation).

If the extract corresponds to the requirements, add 0.40 % tricresol and caramel solution to obtain the desired color. Filter through paper and Seitz filters K3, K5 and ~~MX~~ into sterile flasks.

Campiol (Extract of pyrethrum flowers)

The flowers are ground in a mill without a sieve; then ground again to pass through a 1 mm. slit sieve.

150kg ground flowers are extracted 4 times in an aluminum kettle with petroleum ether 60-80° at 45°C; once for 4 hours with 500 liters, 3 times for 3 hours with 300 l. portions. Total volume of petroleum ether 1400 l.

Evaporate the combined extracts without vacuum to 10 l., wash the evaporation pan with 10 l. petroleum ether and combine with the extract, filter, determine dry residue, and remove solvent in vacuo. Extract the residue 10 times with 40 l. portions of 90 % methanol at room temperature, using rapid stirring. Total volume methanol 1400 l. Discard the residue. Keep the methanol extract at 0°C overnight and filter the next morning. Evaporate the filtrate in vacuo to remove the methanol and take up with 10 l. of toluene-alcohol. Keep overnight at 0°C, filter, and determine pyrethrum. From extracted flowers about 50 l. petroleum ether may be recovered by steam distillation.

Loss of solvent - 200 l. petroleum ether
60 l. methanol

Yield 1.0-2.0 per cent.

Preparation of Campiol Solution.

3.0 kg extract of pyrethrum flowers, calculated on dry residue, dissolved in ethanol, dilute to 100 l. with ethanol containing 0.75 kg lecithin ex ovo. Heat to 50° and stir into 300 l. distilled water at 50°C. Evaporate in vacuo to 150 l. add 100 l. distilled water and evaporate again to 150 liters. Filter through cloth and add water to make 300 liters.

Taste-Correcting Solution

Stir 3.0 kg agar-agar in 100 l. water and leave to swell for 12 hours, then add 100 liters water and 250 kg sugar. Boil with 4 kg sodium benzoate, cool and add 1.0 kg citric acid, 50 kg orange juice, 2 kg orange essence, 1 kg citrus oil and 3 kg recryst. Texapon dissolved in water. Add water with stirring to make 700 liters. Stir for 2 hours.

700 l. taste correcting solution are poured in a thin stream into 300 l. pyrethrum solution. Stir for 2 hours, strain and fill.

Raw Heparin.

To 40 kg dried lungs (well desiccated) add 140 l. tap water, stir well and add 8.4 l. 80 % acetic acid and continue stirring for 1 $\frac{1}{2}$ hours. Centrifuge and reject the solution. Treat the residue in the same manner with 100 liters of permuntit softened water and the same quantity of acetic acid, then centrifuge. Now mix the residue with 100 l. softened water, adjust with Na OH to pH 9.0, stir for 1 $\frac{1}{2}$ hours and readjust the pH to 9 at intervals of 5 minutes by the addition of small quantities of Na OH; a total of about 7 $\frac{1}{2}$ kg. Centrifuge and keep the extract (I); extract the residue twice with dilute NaOH in the same manner, combine extracts I and II. Extract III is handled separately. The pH of the fluid must be 9.0. Test with phenolphthalein paper.

Acidify the combined extracts with acetic acid until weakly red to litmus, filter through cloth and evaporate in vacuo to about 20 liters. Add sufficient methanol to the concentrate so that the methanol content is at least 70 %. Ethanol may be also used. Allow the solids to settle, decant, break into nut-size pieces and extract for 30 hours in a Soxhlet with methanol. Dry and grind.

Preparation of Vetren.

20 kg of raw heparin are stirred with 200 liters of water adjusted to a pH of 1.9 with HCl. Add 20 gm Pepsin 1:10.000 and digest at 38 C for 24 hours. Neutralize, heat to boiling for $\frac{1}{2}$ hour, cool to room temperature, centrifuge and ppt. the clear solution with Me OH. Various fractions of different degrees of purity are obtained which

are combined in accordance with their biological activity and further re-precipitated with Me OH. If a batch is clearly soluble in water and has a strength 2-2½ times the working standard (50 units standard Heparin in 1 cc. 0.9 % Na Cl solution prevents the coagulation of 4 cc. goat blood at 37°C for 1 hour), purification with Eponit is applied. For this purpose dissolve the heparin in 10 parts H₂O, add HCl to a pH 4.0, add a equal quantity Eponit, keep at 60° for half an hour, centrifuge to remove the charcoal and ppt. the solution with Me OH. The heparin obtained has a potency of 3-3½ times the working standard, is pure and free from side effects. It is assayed by animal experiments.

To prepare Vetren or Thrombo-Vetren it is dissolved in 0.9 % Na Cl solution to give 3 mg. or 50 mg Heparin work standard per cc. Fill into ampules. The pH must be 6.5 - 6.8.

Preparation of Phyormon.

10 g. of posterior pituitary powder containing 1000 units/g., are quickly heated to boiling in 1 l. 0.3 % HAC; cool quickly and add 0.1 % benzoic acid and 0.01 % Niposol, leave standing for a day, filter and then filter through a bacteriological filter. Extract contains 8 V.U. 1 cc., adjust to 2 VUigthiin units/cc or for "forte" to 4 units/cc.

Preparation of Praephysyon.

1.8 kg. anterior pituitary powder from hogs are stirred with 10 l. water and a mixture of 0.92 l. N/ Na OH in 9.08 l. of water added. Now add 40 l. water and after 10 minutes slowly add with constant stirring 13 l. n/HAC until the pH is 3.7-3.8., and centrifuge. The ppt. may be used for preparing Prolactin. Evaporate the solution in *vacuo* to about 20 l., add 30 % NaOH to pH 7.1-7.2, and add water to make 25 liters. Add 96 cc. tricresol, keep for at least 8 days at room temperature and filter through folded 560, then through Seitz EX. The solution should not give any reaction with sulfosalicylic acid and has a dry residue of about 1.6 g/100 cc; ash 1.0 g/100 cc. It is ready for filling into ampules. For the preparation of Praephysyon forte, the solution is concentrated three times. The dry residue/cc and ash are then correspondingly increased.

Prolacton.

The insoluble residue of the proceeding process is taken up on 30 times its weight of 66 2/3 % acetone with due consideration to the water content; working at pH 2.0. The prolacton dissolves and may be separated from the insoluble portion by centrifuging. Adjust the clear solution to 90 % acetone and separate the pptd. prolacton by centrifuging, wash with acetone and ether; dry in vacuo.

Yield 15 to 45 g/kg pituitary powder.
30-50 pigeon units/mg.

List of Effective Patents Held by Promonta.

Method of obtaining proteolytic protective ferments. D.R.P. 743,986
Method of obtaining protective ferments. D.R.P. 443,147.
Method of increasing the activity of protective ferments. D.R.P. 742,192.
Method of obtaining protective ferments from Urine. D.R.P. 737,689,
Method of preparing stable organo iron compounds. D.R.P. 682,875.
Method of preparing pharmacologically effective iron combinations.
D.R.P. 665,778.
Process for the purification of heparin solutions. D.R.P. 712,564.
Process for obtaining a blood anticoagulant. D.R.P. 671,746.
Process of obtaining material having blood anticoagulant properties
from plant phosphatides. D.R.P. 686,794.
Process for obtaining gall rich, water soluble organ extracts.
D.R.P. 631,121.
Process for obtaining gall rich lecithin-cholesterin preparations.
D.R.P. 734,403.
The preparation of valuable, physiologically effective materials from
slaughter-house by-products. D.R.P. 624,894.
Rheumitron (salt of salicylic acid). D.R.P. 561,523.
D.R.P. 582,148.
Chalk preparation, D.R.P. 564,610.
Shaving aid. D.R.P. 693,027.
Method for the preparation of soluble cholesterin compounds. D.R.P. 523,
144.
Sestron (Bis-phenylpropylethylamine). D.R.P. 617,647.
D.R.P. 623,593.

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3. Riedel-de Haen, A.G., Hamburg Plant, Hamburg.

The team interviewed W. Mueller and Hans Dieckmann, managers who were very cooperative and anxious to submit all information requested. The Hamburg plant of this company was acquired in 1928 from the firm of Fritzsche Brothers, Leipzig. Formerly the production facilities of the plant were utilized for the manufacture of perfumes for the soap industry; the new owners continued to fabricate the same line of products. At the time of our visit, the

remaining production facilities were being prepared for the synthesis of some pharmaceutical chemicals, such as Chinosol and Barbital, which were formerly made at the Berlin works. The technical direction of Riedel-de Haén was confined solely to the Berlin laboratories, consequently the Hamburg plant had no research staff. Materials used in the production of chemicals were, to a large extent, purchased from the I.G. Farbenindustrie.

Real estate and number of buildings:-

40.000 square meters of land

10 buildings stated to be in condition of manufacturing
11 buildings totally destroyed.

Although ten buildings are intact or have been repaired, the bulk of heavy manufacturing equipment was contained in the destroyed units. The remaining buildings are in a bad state of repair and the equipment appeared to be suitable for small scale operations, but most of it is old and obsolete. The physical condition of the buildings and equipment seen at Hamburg seems to prevail at other plants as well (see, Riedel-de Haén, Seelze).

The Hamburg managers of the firm are:-

Hans Dieckmann

Dr. Hans Puttfarcken

The number of employees at present are:-

Clerical force - 28

Factory workers - 45

Products, Raw Materials, and Manufacturing Schedules:

In reply to questions submitted with reference to the resumption of operations, the managers were inclined to be, in our opinion, unduly optimistic. The equipment and intact factory space appeared to be inadequate to meet the production schedule prepared by Herr Dieckmann and described in detail below:-

Product	Monthly Production	1942 Production(monthly)	Raw Materials required.
Bornyl-acetate (pine needle oil)	2000 kg	2500 kg	6000 kg Turpentine 700 kg Acetic acid
Barbital	500 kg	---	100 kg Sodium metal 600 kg Ethyl bromide 500 kg Urea 2000 kg Monochloroacetic acid
Salicylic acid	500 kg	300 kg	350 kg borneol 425 kg Methyl-salicylic acid
Potassium oxy- quinoline sulphate (Chinosol)	1000 kg	---	500 kg O-anisidine 1200 kg glycerine 30° 200 kg sulfuric acid 66° Be 600 kg potassium sulfate
Chlor-brom-oxy- quinoline	500 kg	2000 kg	350 kg oxyquinoline 160 kg Bromine 750 kg sodium barcarbonate 125 kg sodium chlorate
Perfume oil for soap	3000 kg		
Aldehyde C 16 for essences	100 kg		(2194 kg Acetophonone (3098 kg Cl CH ₂ CO ₂ H (1837 kg Na metal (775 kg Benzol (72 kg Denat. ethanol - <u>Yield 2500 kg</u>
Diacetyl (concentrat- ed butter flavor) D.R.P. 597,256	500 kg		

Product	Monthly Production	1942 Production(monthly)	Raw Materials required.
Concentrated essences for foods	1000 kg		(1800 kg methylethyl ketone (2500 kg sodium nitrite 5500 kg hydrochloric acid
Oils for artificial spices			
Cardamon	1000 kg		
Cinnamon			Terpinyl acetate, cinnamic aldehyde.

Existing facilities for chemical manufacturing cannot be used until supplies of coal and industrial heating gas are available. Supplies of raw materials were not considered to be a serious factor.

4. C. H. Boehringer Sohn, Hamburg.

This plant is a branch of C. H. Boehringer Sohn, Chemische Fabrik, Ingelheim am Rhein.

The Hamburg plant makes alkaloids from natural sources and transforms some of them into well-known derivatives. The plant is in fairly good condition, but needs a few minor repairs to operate. A permit for such repairs should be in order. In addition, to their alkaloid work, they also make a few baking articles (see list of products). This work on food products was reported to a SHAFF food expert in Hamburg, and a subsequent investigation was made by him.

Persons interviewed were Dr. H. Schenkenberger, chemist, C. Langer, T. Büren, and H. Facht.

This plant was built in 1923-1924. The real estate consists of 7000 square meters of which 1000 sq m. is leased to the firm of Dijkeroff and Witmann, a construction company.

The names of the chief managers are:-

Dr. H. Schenkenberger, chemist
Theodor Büren, engineer
Hasso von Hann, merchant

The number of employees are:-

23 men
20 women
51 working women
56 workmen
13 apprentices

Products made by C. H. Boehringer Sohn.

<u>Preparations</u>	<u>Chemical Names</u>	<u>Application</u>
Opium powder		
Opium extract		
Opium tincture		
Morphine & its salts		
Codeine & its salts		
Aethylmorphine & salts		
Diacetylmorphine & salts		
Papaverine		Antispasmodicum
Narcotine		soft sedative
Thebaine		raw material f. Acetidicon stimulantia
Caffeine		cardiaticum
Theobromine		
Morphine - ampules		narcoticum
Caffeine natr. benz-ampules		cardiaticum
Lobelin "Ingelheim" (Lobeton)ampules	synthetic pure alkaloid of Lobelia inflata	for intensive stimulation of respiration

<u>Preparations</u>	<u>Chemical Names</u>	<u>Application</u>
Sympatol	Para-methylaminoethanol-phenol tartrate	for heart and blood-circulation.
In addition there is a warehouse for preparations produced in the Ingelheim/Rhine plant.		
Acedicon tabloids	Acetyl demethylodihydrothebain hydrochloride	strong cough remedy
Adrianol Emulsion	1-m-methyleaminoethanol-phenol hydrochloride	Anti Rinitis
Aludrin solution and tablets	Dioxyphenylaethanol isopropylamine sulfate	Asthma bronchiale
Bilival pills	Lecithine & sodium chocolate	liver and bile remedy
Codyl Syrup	Syrup with codeine, narctine and papaverine	cough remedy
Euxanthin	Theophilline and camphor-cholic acid	heart and blood circulation remedy for aged
Lacalut, das medizinische	salt of lactic acid	for treating gums and teeth
Mundpulver		
Ropal	Calcium acetate	against decomposition of bread

Baking articles produced in Hamburg.

Lecifarín	Flour treated with lecithin	bread baking improvement
Boeson 8	Flour treated with lactic acid	bread baking improvement
Lecisauer	Flour treated with lactic acid and lecithin	bread baking improvement
Backsyrol	Lactic acid preparation	baking improvement for westphalian rye-bread
Boerol	Lactic acid preparation	to improve fermentation
Boeson Backpulver	oil and water emulsion	baking powder to prepare pans for baking and to separate ready baked bread from pans.
Trennemulsion		

Producing Capacity of the Factory

Monthly output of essential products:

A	Opium - alkaloids corresponding to all pharmacopoeias: Morph.Hydr. or Codein (methylmorphine) pure and salts or Ethylmorphine hydr.; Diamorphine hydrochloride	summa 300.-kg
	Narcotine hydrochloride	200.-kg
	Papverine, output from opium-manufacture or purification from synthetic raw-papaverine manufacture	100.-kg
	Thebaine, according to the extent of Opium	
B.	Opium preparations:	
	Opium powder, corresp. to all pharmacopoeias	400.-kg
	Tincture of Opium Dto.	500.-kg
	Extract of Opium, dry or liquid, Dt.	25.-kg
C.	Purification of Caffeine from raw-caffeine	3000.-kg
	Caffeine sodium benzoate or Caffeine sodium salicylate	1000.-kg
	Theobromine and it's salts	1000.-kg
D.	Specialities:	
	Sympatol or Lobelin or Morphine or Caffeine sodium benzoate ampules	600000 amp.
	Sympatol liquid	250000 flasks

Possible figures of production for the next 6 months:

A-	Opium alkaloids:	100.-kg
	Morphine and it's derivates	100.-kg
	Narcotine hydrochloride	25.-kg
	Papaverine hydrochloride	
B.	Opium preparations:	
	Opium powder	200.-kg
	Tincture of Opium	200.-kg
	Extract of opium	15.-kg
C.	Caffeine and it's salts	500.-kg
	Theobromine and it's salts	200.-kg
D.	Specialities:	
	Sympatol or Morphine hydrochloride or Caffeine sodium Benzoate or Caffeine salicylate ampules	100000 amp.
	Sympatol liquid	30000 flasks.

Manufacturing Methods.

1. Manufacture of Morphine from Opium
2. Morphine from poppy capsules
3. Secondary alkaloids
4. Narcotine HCl
5. Papaverine
6. Papaverine - HCl
7. Codeine and thebaine
8. Codeine by methylation of morphine
9. Codeine HCl
10. Codeine phosphate
11. Acetyl morphine from morphine
12. Diamorphine from morphine
13. Theobromine from cocoa residues.

1. Morphine from Opium.

Mix 6 boxes of opium - 450-480 kg. (Turkish or Persian) in a mixing machine (1000 ltr. capacity) with 40-60 liters hot H_2O , and keep at 40-60°. After 1 hour add 8-9 kg. $Na H CO_3$, to neutralize (litmus), 5 hours of mixing necessary. Cool to 16-18° and add 100 ltr. Methylene chloride; after 45 min. of mixing, again add 200 ltr Methylene chloride. After 2 hours leave at rest for settling out and strain through a sieve. Repeat this extraction 5 times. The $CH_2 Cl_2$ extracts 1-4 are evaporated in a still with stirrer. The residue contains gum, narcotine and papaverine, and also small quantities of codeine and thebaine. It is handled separately. Extracts 5 and 6 are used in preparing extracts 1 and 2 of the following batch.

The opium paste in the mixing machine is freed from CH_2Cl_2 by distillation; towards the end, vacuum is used. Then dilute with water to thin consistency, so that the mixture can be poured into 500 ltr. copper vessels. Heat to boiling, then cool with metal coils to 16-18°. Divide into 2 parts. The half batch (225-240 kg. Opium) is mixed in a wooden tank with stirrer with 70 kg. $\text{Ca}(\text{OH})_2$ and 1200 liters H_2O . Stir for 1 hour. Filter through a wooden filter press. Extract the alkaline liquid twice with C_6H_6 , to obtain Codeine and Thebaine.

Remove the C_6H_6 by distillation and collect the residue from 1400-1900 kg. opium for working over again. Neutralize the alkaline liquid in a container of 2000 ltr. capacity with stirrer, using H Cl until it is very weakly alkaline to phenolphthaleine. The main portion of morphine precipitates out. Separate it on a suction filter from the mother liquid and wash with hot water. Acidify the mother liquid weakly with H_2SO_4 and evaporate in vacuo from 1800-2000 ltr. This is the crude solution.

The alkaline filter residue is suspended in H_2O and acidified with H_2SO_4 . Remove pptd. Ca SO_4 and insol. residues on filter press. This fluid is to be used in the next batch with the 70 kg. $\text{Ca}(\text{OH})_2$ to treat the opium. Extract the press residue repeatedly (up to 5 times) with H_2O and use the fluids in next batches, for extraction of the next stronger fractions; or after a certain accumulation of solids, evaporate in vacuo and add to "crude solution".

The "crude solution" from 15 to 18 boxes of opium amounts to 1500-1800 liters. This is mixed in wooden vessel with $\text{Ca}(\text{OH})_2$ until it is strongly alkaline. Filter Ca SO_4 off in filter press, acidify with H_2SO_4 and evaporate in vacuo. Filter Ca SO_4 off, mix the filtrate with denatured EtOH (ca.15% of the volume of the fluid). Heat and ppt. a further amount of crude material with NH_3 . Cool with occasional stirring and filter by suction.

Extract the mother liquid repeatedly with fusel oil (amyl alcohol) to remove all the morphine. Mix 800 liters mother liquid hot, if necessary by adding Na_2CO_3 , with 2000 l. fusel oil. The latter drains into another mixing vessel, and the morphine is dissolved out of it with hot H_2O & H Cl. The sept. aqueous part is evaporated and the morphine pptd. with NH_3 , adding denatured EtOH. The various fractions of morphine are purified. All end mother liquids and pptg. liquids of the purification process are subject to the same treatment. It may be repeated until no more morphine can be found.

Purification of Crude Morphine.

Dissolve the crude morphine fractions in an enamelled kettle in H Cl (20 kg crude morphine require 150 l. hot H₂O and about 6 ltr. conc. H Cl 40%). Ppt. the morphine from the filtrate with NH₃ and Na OH. Redissolve the morphine pptd. in hot H Cl, add 20% denat. alcohol and reprecipitate. The morphine is now redissolved in hot HCl + H₂O (3 parts moist morphine + 2 parts hot H₂O). The hot morphine solution is treated with charcoal and filtered hot into a dish for crystallization. The morphine - HCl - is centrifuged off, and recrystallized from hot H₂O. From the aqueous solution ppt. the morphine base with NH₃. The morphine base thus obtained is used to make codeine, ethyl morphine and diacetylmorphine. To obtain pure morphine hydrochloride, it is necessary to recrystallize the hydrochloride once or twice, and if necessary reprecipitate with NH₃ + denatured EtOH.

The last crystallizations are not centrifuged, but the mother liquid is removed in a hydraulic press. Final and crystallization is made from an EtOH - Et₂O mixture.

Batch: 32 kg. pressed cake of morphine HCl is dissolved in 2.5 litr. of hot water (enamel kettle) by blowing steam into the mixture. Filter through cotton cloth and add to 85 liters of denatured EtOH. The EtOH contains 200 gr. tartaric acid and 400 g. conc. HCl. While the mixture is stirred, crystallization begins. Add 20 litrs. Et₂O which finishes the crystallization quickly.

Keep standing for a day, and filter by suction, pulling dry very carefully for 12 hours. This is done in a percolator. The contents of the percolator are cut into 10 pieces which are dried slowly at 30°. The hard crust is scraped off and the interior part either cut into cubes or pulverized. Yield - 90% of morphine, analysis according to Harrison & Salves.

Morphine from Papaver Capsule-shells.

Dry capsules are ground in a snail mixer, mixed with H₂O or extract, until thoroughly moist. Fill into tanks, provided with sieves at the bottom. 8 tanks of 2000 l. capacity are used, each filter with 1000 kg. capsule shells. Extract by adding to tank I fresh water, that is sprinkled evenly on the surface. When the tank is filled, drain from bottom with a small pump, and pour on tank II. Thus all tanks are filled. The speed of water run is 2000 l/hour. From the third tank on, 3000 liters are drawn off into a collecting tank, the next 2000-3000 liters extract are used for the preliminary

wetting of the capsules. The exhausted material may be used as a fertilizer. The strong extract is heated with stirring, to ppt. proteins, then evaporated in vacuo to syrup consistency.

1000 kg. of the concentrate mix with 100 kg. Na_2CO_3 in a kettle with stirrer and stir with 6000-7000 ltr. ethylene chloride. Heat to the boiling of the latter. Stop stirrer and leave 2 hours for settling. Decant clear solution in lead coated stirring equipment, in which the cooled liquid is extracted with dilute H_2SO_4 , which extracts the alkaloids. An average of 3 extractions with ethylene chloride are sufficient.

Secondary Alkaloids.

The residue of the methylene chloride extracts of opium contains, as mentioned, gums and narcotine and papaverine, also traces of codeine and thebaine. The residue is stirred and heated with 800 ltrs. H_2O + 12 ltrs. 20% H_2SO_4 . The CH_2Cl_2 evaporates. After cooling to 50°C, drain into wooden tank of 1000 liters. with 3 decanting faucets. After settling, drain the acid solution off from the gum. The residue is reheated with 700 ltr. H_2O again. This second extract is used as first extracting fluid in the following extraction. The first H_2SO_4 ext. is hot mixed with dil. NaOH until weakly acid: The crude narcotine is pptd. and filtered by suction on a clay filter. The mother liquid is now weakly alkalized (litmus), which ppts. the papaverine. The mother liquid is then strongly alkalized and extd. with C_6H_6 to obtain codeine and thebaine. The duration of the extraction is regulated according to tests in the control laboratory. The benzene is distilled off and is added to the benzene extract from the alk. $\text{Ca}(\text{OH})_2$ opium liquid, to be worked up with same. The crude narcotine is dissolved with 5 parts of hot water and HCl , then treated with charcoal and filtered. The base is pptd. from the filtrate with NaOH . This narcotine is filtered by suction and dried at 100° 50 kg. dry crude narcotine are dissolved in 500 ltr. C_6H_6 ; the solution is filtered through a filter containing charcoal and the clear benzene solution is distilled in a stirring tank of enamel. The residue is taken up in 50 ltr. 94% EtOH (hot). The narcotine is obtained from this mixture in thick crystals. It is filtered by suction. Besides narcotine, the alcoholic mother liquid contains some papaverine. The pure narcotine base is used to make the HCl salt.

Narcotine Hydrochloride.

Mix 60 kg. of pure narcotine on a glass-lined 200 ltr. kettle (stirring with 60 ltr. hot denat. EtOH of 99%). Slowly add conc. HCl (38-40% HCl) until acid to Congo red. When all is dissolved filter through cotton into a 150 ltr. enamelled kettle, that is cooled with water from the outside. After some time crystallization begins. Stir the content frequently, taking care that the crystals do not adhere to the walls of the kettle. The following day filter with suction on a stoneware filter, wash with EtOH, acidified with HCl. The moist crystal paste is dried first at 30° later at 60°. Precipitate the narcotine from the mother liquid with NaOH after distilling off the EtOH. This narcotine re-enters the process as crude narcotine.

Papaverine.

The crude papaverine and the alcoholic mother liquid from narcotine, containing papaverine, are combined. Solution is obtained by heating and, if necessary, adding 94% EtOH. Add powdered oxalic acid to Congo acid reaction. During the following days (frequent stirring) papaverine bioxalate crystallizes out. Filter with suction.

Precipitate from the mother liquid with NaOH the narcotine and traces of papaverine. This precipitate is treated as crude narcotine. The papaverine bioxalate is repeatedly recrystallized from 10 parts of hot H₂O, using charcoal, until the kryptopin reaction disappears. Finally the papaverine is pptd, with NaOH and filtered on a stoneware filter. Dry the base at 50°, add benzoic acid and crystallize the benzoate. From this precipitate the pure base with NaOH, filter and wash well with distilled H₂O. Use for papaverine HCl.

Heat the papaverine with 3 parts of 50% EtOH. Add, while stirring, conc. HCl (40%), until acid to litmus. Filter through cotton cloth. Now add HCl until acid to Congo red. Cool while stirring. Filter the following day and wash with EtOH. Dry with precaution.

Codeine and Thebaine from the Benzene Extract

After distilling the C_6H_6 from a total of 1400-1900 kg. opium, heat the residue with 70-80 liters 94% EtOH until a thick syrup is formed. Keep standing for 1-2 days and filter by suction. The residue contains the valueless alkaloids Kryptopin and Protopin. Acidify the filtrate weakly to litmus with H_2SO_4 + EtOH 1:1. After a few days codeine sulfate separates out. Filter and wash with a little EtOH. Add cryst. tartaric acid to the mother liquid until weakly acid. Stir frequently. During the following days thebaine bitartrate separates out. Filter and wash with EtOH. The codeine sulfate is added to the codeine obtained by methylation of morphine. The yield is 0.5 to 1%, depending on the type of opium used. Persian opium contains more codeine.

Mix the thebaine tartrate with 6 parts of H_2O and neutralize at 40° with NH_3 , which effects solution. Treat with charcoal and filter. Add tartaric acid to the filtrate to weaken acid reaction to Congo red. This gives pure thebaine bitartrate. If necessary repeat this operation. Mix the pure bitartrate with H_2O to a thin paste, and then add NH_3 solution (1:1 diluted). Filter the pure thebaine by suction, wash with H_2O , and dry at 40° . The mother liquid of the bi-tartrate purification and from the precipitation are combined and extrd. with C_6H_6 . The C_6H_6 solution is added to the original extr. from opium. Yield 0.2 - 0.8%. Higher yield from Persian opium.

Codeine by Methylation of Morphine.

Preparation of the phenyltrimethyl ammonium chloride.

In a lead lined autoclave wth stirrer treat 300 ltr. dimethylaniline with 40 lg CH_3Cl at 80° . The process takes 16 hours. After cooling, filter dry by suction. Add to the mother liquid fresh dimethylaniline to make 300 ltrs. and use for following batch. First the quaternary ammonium base is prepared by mixing 22 kg. of the methylation salt in 10 ltrs. Me OH with a calculated quantity of 22% K OH in Me OH. A slight excess of methylation salt is necessary. Filter over charcoal, wiegh and adjust using phenolphthalein. Calculate to use for 1 mol of morphine, 1 mol of quaternary base + 15% excess. Place the morphine into an enamel distillation apparatus with Ca 500 ltrs. toluene. Heat to boiling until toluene free from H_2O distils. This serves to remove the H_2O from morphine. Cool to about 20° and get the quaternary ammonium base ready; add first 105% and heat to boiling of the toluene, then at intervals of 10 minutes add the remaining 5 + 5-10%. First Me OH distils, later the toluene. After 2 hours stop the heating and let cool to the following day. Pass

over into a lead lined stirring apparatus of 700 liters and wash twice with 30 ltr. cold H_2O and 300 cc. NaOH of 40° Be to remove products of decomp. and rest of morphine.

Pass the toluene solution into a lead lined distn. apparatus and distil the toluene off with steam.

Add the calc. quantity of dil. H_2SO_4 to neutral reaction and distil the dimethylaniline off with steam. Evaporate to crystn. and pour immediately into an open enamel kettle. After crystallization and cooling, centrifuge. Evaporate the mother liquid for further crystallization. The dirty final solutions are made alkaline with NaOH and the residual codeine is extracted with C_6H_6 . Purify the crude codeine sulfate by crystallization from hot water using charcoal, until colorless. Prepare this paste to codeine sulfate with H_2O and ppt. pure codeine with conc. NH_3 ; filter immediately by suction, wash with water and recrystallize with dil. EtOH. (1 kg. codeine pure - 400 c. EtOH). Dissolve the codeine (suction) after cooling. All residual solutions are acidified with dil. H_2SO_4 , evaporate and added to the purification of crude codeine sulfate.

Codeine Hydrochloride.

Mix 20 kg. moist codeine pure with 80 ltrs. 94% denat. EtOH. Filter into container with cooling equipment and add aqueous conc. HCl until acid to litmus. On cooling the codeine - HCl crystallizes out. Filter on stoneware filter (following day); dry at $40-50^\circ$.

Codeine Phosphate.

Similar to the HCl salt. Mix solution in EtOH with pure conc. H_3PO_4 sp/g 1.7 until acid to litmus. Yield from morphine is 92-95%.

Ethylmorphine.

Similar to Codeine Mfg.

Heat 25 kg. diethylaniline with 24 kg. diethylsulfate for 8 hours to $80-100^\circ$. Cool and add 15 ltrs. abs. EtOH with the

calculated quantity of KOH in EtOH, using a small excess of the reaction fluid diethylaniline - diethylsulfate. Add charcoal and filter. Det. by filtration with phenophthalein the mol. value of the ethylizing fluid as compared to pure morphine and use 15% excess of the former. The other process is the same as in codeine manufacture. The aqueous H_2SO_4 solution of ethylmorphine, after removal of the toluene and diacetylaniline is not evaporated to crystallization, but only so far that, with a batch of 30 kg. morphine approximately the four-fold quantity of aqueous solution is obtained. Filter using charcoal. Precipitate ethyl morphine with conc. NH_3 . Extract residue of ethyl morphine from the liquid with C_6H_6 and add to following batch. The purified ethylmorphine base is transformed into HCl salt. Dissolve in 3 parts 94% EtOH, filter and add HCl to acidity (litmus). When crystallization begins add 12 ltrs. Et_2O to accelerate crystallization, and leave to the following day. Filter by suction and wash with EtOH - Et_2O (1:1). Dry at 40° . If necessary redissolve hot in 80% EtOH and cryst. with Et_2O . Yield 93-96%.

Diamorphine

In a glass-lined tank with stirrer and vent. to the open air, mix 10 kg. morphine base with a mixture of 9 kg. acetic anhydride and 50 kg. acetylchloride. A violent reaction sets in. This may be assuaged by heating mildly 10 kg. morphine base with 12 kg. acetic anhydride for 2 hours. Then cool to $20^\circ C$ and add 30 ltrs. of cold distilled water. By the use of acetylchloride a light yellow solution is obtained; acetic anhydride along gives a bordeaux-red liquid. The solution is precipitated with cold aqueous Na_2CO_3 solution. After filtering with suction dry at $50^\circ C$. Recrystallize twice from 4 parts of ethyl acetate. Evaporate the mother liquids, saponify the residue by adding dil. NaOH and regain the morphine. 5 kg. purified diamorphine are mixed with 20 ltrs. ethyl acetate and neutralized with 25% HCl (litmus). By working fast, a solution is obtained temporarily. After cooling suck dry on the next day and dry the product at $40-50^\circ C$. Saponify the mother liquid for morphine. Yield 95-97%.

Theobromine from Cocos Residues.

Mix the defatted residues with 15-20 % CaO powder. In the same mixer add H_2O or extracting fluid until an even consistency

is obtained with about 25% moisture. The mixture becomes warm and releases NH_3 .

In a stirring tank stir for 1 hour with 1200-1500 liters of water or extracting fluid per 1000 kg. cocoa powder. Then let settle out; this requires some time. Decant the clear liquid, and, if it is a strong extract, transfer to stirring tanks for the precipitation of the theobromine. Since the cocoa material is extracted 2-3 times with liquid, as described, 1 or 2 weaker extracts are obtained, which according to the counter-current principle are used in the following batch.

The exhausted material is centrifuged and may be used as a fertilizer.

The strong extracts are cooled and slightly acidified with HCl, with slow stirring. The crude theobromine is withdrawn from the bottom of the tanks and transferred to a container for further settling out. The crude matter is stirred with water and so much $\text{Ca}(\text{OH})_2$ until the theobromine is dissolved. During this process, heat and then filter the hot liquid through a filter press. Acidify the filtrate with HCl and centrifuge after cooling. All mother liquids are returned to the manufacture. The techn. Theobrine is dissolved in NaOH ptd. with H_2SO_4 while hot, keeping the liquid always alkaline. Yield 75%. Analyt. det. in conformity with Pharm. Ztg. 67 of 20.8. 1930.

5. Nordmark-Werke, G.m.b.H., Hamburg. Betriebswerk Uetersen/Holstein

This plant manufactures medical products such as liver extracts, vitamin preparations, sulfa drugs, hormones from glands, and enzyme preparations. It was located originally in Hamburg, but in 1939 it was moved to Uetersen. The buildings and equipment are in good condition. In fact, this plant appeared to us to be the best one we visited on our trip through northern Germany as regards buildings, lack of damage and equipment.

The Directors of this plant are:- Alfred Voss and Julius Wolf. The persons interviewe were:- Dr. R. Neurauter, Julius Wolf, Dr. W. Loop, Dr. W. Trumpelt and Dr. H. Brender. These men constitute the scientific staff. (We did not see the other member of this staff who was, Marie-Luise Schütt). Thses men were very cooperative and did not hesitate to answer questions.

Particulars of share capital and by whom held:-

Share capital - 2,580.000 marks

Held by A. Voss - 52 %

Held by J. Wolf - 48 %

The estimated gross sales were about 12.000.000 marks yearly. The real estate consists of 120.000 sq m. The factory consists of eight large buildings and a few small auxiliary buildings consisting of 17.000 sq m. This plant has stocks of raw material sufficient for three months production. The ware houses contain manufactured goods with a value of 500.000 marks. Approximately 250 persons are employed in this plant.

Research Activities.

During the war this group has carried out research on the following subjects.

1. Penicillin.

The studies on penicillin, carried on for about one year, never progressed beyond the stage of testing the culture fluid. The original culture of penicillium, and a mucor strain, were obtained from Frau Professor Stoppel of Hamburg, who was not available for interrogation. The work was done in flasks. Some strains were found which exerted a growth inhibiting effect on certain bacteria, e.g., Corynebacterium diphtheriae. The strains tended to loose their potency over a period of time. This group was not familiar with the work done on penicillin in England and America.

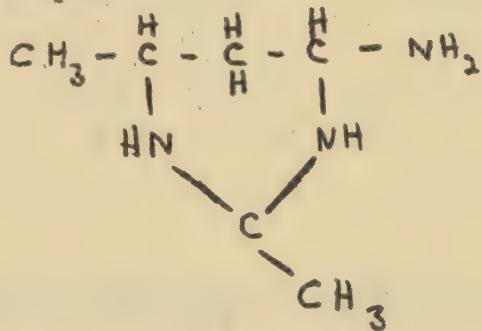
2. Protein Digests

This group prepared digests of casein and whole blood. The digestion was carried out first with pepsin at pH 2.8-3, followed by tryptic digestion at pH 8 at 40°C for 24-48 hours. The acidity was obtained with sulfuric acid supplemented with small quantities of hydrochloric acid at the end. The sulfate iron was removed later with calcium carbonate. Tryptic activity was destroyed by heating the digest to 100°C. Histamine-like substances were partially removed by extraction with benzene (C₆H₆). The digest was filtered, diluted to 1 % total nitrogen content and sterilized by heating to 80°C for two hours on three consecutive days. The solutions were checked only for histamine effect. A few clinical tests were carried out; these were not satisfactory, however, histamine shock being produced.

3. Sulfa Drugs.

a) 4(Sulfanilamido) 2,6-dimethyl-pyrimidin.

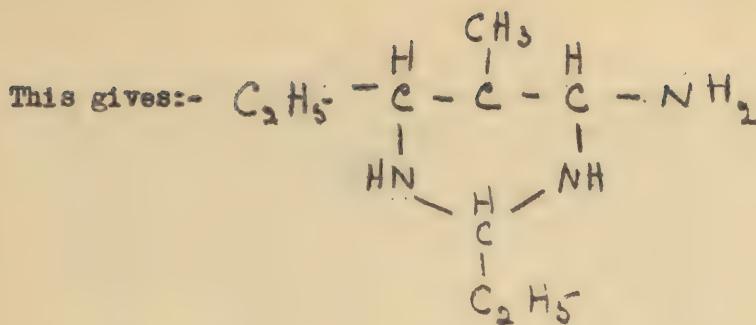
Treatment of acetonitrile with metallic sodium gives the pyrimidine compound -



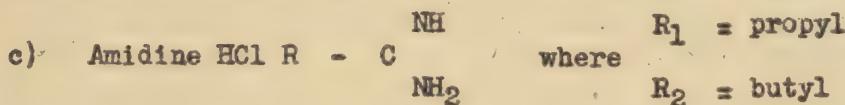
This compound condensed with Cl SO₂ -  AC in CH₂Cl₂ solution. Trimethylamine in benzene solution is used as a catalyst. The acetyl group is split off by alkaline hydrolysis.

b) 4-(Sulfanilamido) 2,6-diethyl-5-methylpyrimidine.

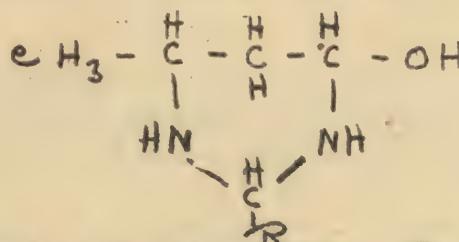
Propionitrile is used in place of acetonitrile.



condensation is carried out as described under (a) above.



Heated with acetoacetic ester + Na gives:-



The OH is replaced by Cl using PCl_3 . The Cl compound is condensed with acetyl sulfonamide by melting, using copper or phosphorus bronce (alloy) as catalyst. Sodium carbonate is used to absorb the chlorine.

In animal experiments it was found that the toxicity of 4-(Sulfanilamide) 2,6-dimethylpyrimidine was small when compared with known sulfonamides. In streptococcal infection, the efficacy was greater than that of sulfapyridine. Clinical tests showed this product to be the best tolerated sulfanamide derivatives. However, it resembled sulfapyridine.

The 4-(Sulfanilamide) 2,6-diethyl-5-methylpyrimidine showed little toxicity in animals, but greater than with the dimethyl compound. In experimental pneumococcal infection of the mouse the effect with the diethyl compound was better than with sulfapyridine. Exceptionally high blood concentrations were obtained with this compound. Clinically it was efficacious with far smaller doses than with sulfonamide, and appeared to be about equal to sulfapyridine in pneumococcal, streptococcal and meningococcal infections. It was not suitable for the treatment of gonorrhea.

Two other sulfanilamide derivatives were prepared by this group and tested on animals. They were 4-(Sulfanilamido)-2-ethyl-6-methylpyrimidine and 4-(Sulfanilamido)-2-propyl-6-methylpyrimidine. Both compounds were found to be more toxic than sulfapyridine, but the efficiency in streptococccic infection of the mouse was better than that of 4-(Sulfanilamido)-2-6dimethylpyrimidine. In pneumococccic infection of the mouse they seemed to be better than sulfapyridine. No clinical testing was carried out with these compounds.

This group has also studied the increase in solubility, and detoxification of sulfanilamide derivatives. They have prepared sulfamilglucosamide and N^1 - glucosides of sulfanamides with hydrolysis mixtures of lactose sucrose.

They have also made preparations of N^1 - p-aminobenzene-sulfonamide-pyridine-quinoline and isoquinoline derivatives.

4 Anthelmintics.

Preliminary tests on para-amino-benzenesulfonamidothymol against oxyuriasis indicated the substance to have some promise as an anthelmintic.

5 Hexestrol

Research designed to discover an improved method of producing hexestrol has produced nothing significant. The method investigated is the Wurtz coupling (using Mg, or Zn) of a-brom(or chloro)-2-(p-methoxyphenyl)-n-propane. This is a known method which has given only small yields of the required substance.

6 A vitamin-iron preparation to increase the iron content of cow's milk for infant feeding. The preparation facilitates simultaneously the fine flocculation of milk. It contains bivalent iron, Vitamin C and pepsin-glutamic acid HCl. Patent applied for N 47.910 IV a 153 i.

7. Preparation of disinfectants containing mercury. They prepared pyridylmercuric chloride and its salts, aminopyridylmercuric chloride and its salts, and complex Hg-pyridine salts. Pyridylmercuric chloride was found to have an excellent bactericidal potency.

This was shown especially against staphylococci and streptococci where it was found to be superior to H_2Cl_2 by about 100 times. It appeared to be effective against anthrax. The compound itself is not new, but the patent application N 47 800 IV c/120 deals with a new method of manufacture.

8. Preparation of halogen-nitro-naphthalene compounds to be used as weed destroyers.

9. Stable water-soluble vitamin K preparations. The sodium salt of 1-hydroxy-2-methyl-4-acetaminonaphthalene was found to have good antihemorrhagic properties after intravenous injection. Patent application N 47651 IV c/129.

10. In a search for new sources of Vitamin A or carotene the pigment of rose hips was investigated. A publication on this subject appeared in Pharmaceutische Zentralhalle Für Deutschland No.19/27, 1944.

11. Blood Anticoagulants.

At the suggestion of Professor Maurer of Rostock, the sodium salt of a di-sulfuric acid ester of a 20% carboxylated cellulose was prepared and tested in animals for its anticoagulant action. This and similar substances were found to be similar to heparin in this respect, but slightly more toxic. Patent application M 159784 IV c/120. This sodium salt of the sulfuric acid ester of alginic acid was also prepared. It showed a good anticoagulant effect, but of short duration. Patent application N 47920 IV a/30 H.

12. Apparatus for Blood Transfusion.

This apparatus consists of a tube the inside of which is coated with a clotting inhibiting layer. The blood is obtained by venipuncture whereby the blood flows from the needle into the receptor tube. By the same method, the blood is transmitted directly with the hypodermic needle to the recipient. The inflow and outflow of the blood is regulated by a rubber ball air pump, which produces either suction or pressure. The apparatus makes possible a transfusion when

donor and recipient are not in the same room (Austrian patent 146698).

13. Method of manufacture of Hematoporphyrine. Patent application No. 46656 IV c/122p.

14. Method of manufacture of aldehyde acids and oxyaldehydes. Patent application No. M 153381 IV d/120.

15. Method of preparing protein from blood by treating blood with H_2O_2 or with ozone or ozone-oxygen mixtures for the purpose of dechlorizing.

Special Equipment.

This firm had several machines of very good qualities to cut, fill and seal ampules. These machines are manufactured by Luigi Marzocchi, Milan, Italy.

Products Manufactured by Nordmark.

1. <u>Aktivanad</u>	Contains liver extracts, glycocoll, hematoporphyrin, iron, plant substance, Vitamin B and Vitamin C.
2. <u>Aktivanad for Children.</u>	Contains liver extract, glycocoll, Vitamin C, and iron in the form of 20% Ce-Ferro juice.
3. <u>Anginotrat</u>	Vitamin C - bismuth iodine.
4. <u>Arsen-Hepatrat</u>	Liver extract with As_2O_3
5. <u>B₁-Hepatrat</u>	Liver extract and Vitamin B ₁
6. <u>Beta-cholin</u>	Vitamin B ₁ and acetylcholinchloride.
7. <u>Be-Vitrat</u>	Vitamin B concentrate.

8.	<u>Dis-Be-Vitrat</u>	Mixture of natural Vitamin B and C complex.
9.	<u>Calcium-Nordmark-Tabletten</u>	Calcium and phosphorus in combination with glutamic acid HCl
10.	<u>Calcium-Nordmark ad Injectionem.</u>	Calcium gluconate or calcium levulinate.
11.	<u>Cardiotrat</u>	Quinidine nitrate, phenyl-ethylbarbituric acid and circulatory active substances.
12.	<u>Ce-Ferro</u>	Ferrous iron with Vitamin C and sulphhydride compounds.
13.	<u>Chinin-Calcium-Nordmark</u>	Basic quinine plus calcium levulinate.
14.	<u>Citrosulf</u>	Sulphydril sulfur in combination with a pyrazolon complex.
15.	<u>Cortineurin</u>	Cortical extract in combination with Vitamin B ₁ (Co-carboxylase) and Vitamin C.
16.	<u>Due dentrat</u>	Heterocyclic amino acids from stomach and duodenum and Vitamin C.
17.	<u>Elastonon</u>	d-L- <i>B</i> -phenylisopropylamine-sulfate.
18.	<u>Enzymon</u> .	Enzyme preparation containing the Castle factor from stomach linings.
19.	<u>Eubasinum</u>	d-(<i>c</i> -aminophenylsulfonamido)-pyridine-sulfapyridine.
20.	<u>Eubasinum Solubile</u>	Solution of sodium salt of above compound
21.	<u>Eubasinum-Streupulin Powder</u>	
22.	<u>Eubasinum-Salve</u>	Ointment
23.	<u>E-Vitrat</u>	Vitamin E concentrate.

24	<u>Ferro-Hepatrat</u>	Liver extract with Vitamin C and a ferrous salt.
25	<u>Fructamin</u>	Vitamin C and P complex
26	<u>Glyconorm</u>	Mixture of extracts of the adrenal cortex, meat and liver with Vitamin B ₁ , B ₂ , nicotinic acid, Vitamin C and amino acids.
27	<u>Glykokoll-Nordmark</u>	Glycocol
28	<u>Hämostaticum-Nordmark</u>	1.5% Congo red solution
29	<u>Hepatrat Liver Extract</u>	Liver plus stomach extract rich in intrinsic factor
30	<u>Hornodyn</u>	Cysteine
31	<u>Hornodyn-Natrium</u>	Vitamin C, cysteine, glycocol, glutamic acid and NaCl.
32	<u>Kationorm</u>	Ca, Mg, K salts for electrolytic therapy.
33	<u>Linctusal</u>	Chiefly primulae saponins and ephedrin.
34	<u>Mucin comp.-Nordmark</u>	Mucin from stomach lining with histidine, Vitamins B and C and plant protein.
35	<u>Belladonna-Mucin</u>	Mucin plus belladonna extract
36	<u>Mucotrat</u>	Dried stomach preparation
37	<u>Myotrat-cps.Pillen</u>	Muscle extract, quinine, benzylbenzoate, and phenylethylbarbituric acid
38	<u>Neo-Hepatrat</u>	Liver preparation
39	<u>Nucleotrat</u>	Pentosenucleotid
40	<u>Ominval</u>	Vitamins A and D of cod-liver oil plus Vitamins B and C
41	<u>P-Vitamin-Nordmark</u>	Permeability vitamin
42	<u>Photodyn</u>	Hematoporphyrin-Nencki

43	<u>Sedatif-Nordmark</u>	Extract of Passiflora incarnata and Crataegus, potassium phenyl-arsenite, and Ca and Mg bromides.
44	<u>Soluga</u>	Contains lecithin, protein, calcium, Vitamin B and C, and lemon fruit
45	<u>Splenotrat</u>	Spleen extract
46	<u>Teststrat</u>	Testicular extract
47	<u>Titro-Salz</u>	Contains organic and inorganic Na,K,Ca and Mg salts
48	<u>Titro-Salz ad Infusionem</u>	Sterile infusion salt mixture of NaCL, Ca,Mg and K salt
49	<u>Titro-Salz Spezial</u>	Chloride free salt mixture contains no organic Na, Ca, K and Mg salts.
50	<u>Valotrat</u>	Diethyl amide of valeric acid
51	<u>Zentropil</u>	Sodium salt of diphenylhydantoin.

Monthly Production of Important Preparations.

Betacholin-Ampullen	18.00	ltr.
Calcium Nordmark Ampullen	700.00	"
Calcium Nordmark Tabletten	250.00	kg
Chinin Calcium Nordmark Ampullen	10.00	ltr
Cortineurin Ampullen	57.00	"
Duodentrat Ampullen	30.00	"
Elastonon Tabletten	2.00	kg
Elastonon Tropfen	10.00	ltr
Enzynorm Bohnen	700.00	kg
Enzynorm Pulver	750.00	"
Enzynorm Liquid	8000.00	ltr.
Eubasinum Substanz ca. davon Tabletten	3000.00	kg
" Pferdetabletten	1995.00	kg
" Wundstreupulver	460.00	"
" Zäpfchen	1875.00	"
" Ampullen	15000.00	Stück
	1200	ltr.

Hepatrat Amp., einschl. Arsen-Hepa, etc.,	
	1500.00 ltr.
Heatrat Bohmen	750.00 kg
Hormodyn Amp.	20.00 ltr
Hormodyn Pillen	20.00 kg
Hormodyn Natrium Körner	30.00 "
Mucin Pulver	1000.00 "
Nocleotrat Amp.	150.00 ltr
Omnival	1500.00 "
P Vitamin Amp.	20.00 "
Photodyn Amp.	130.00 "
Photodyn Tropfen	200.00 "
Zentropil Tabletten	50.00 kg

Methods of Preparation of the Important Products.

Acetylcholine Chloride.

Reflux 15 g. choline chloride and 100 cc. acetic anhydride for 2 hours. After cooling remove the acetic anhydride in vacuo; filter with suction and wash with acetone.

Betacholin

Acetylcholine chloride	5.0	%
Aneurin (Vit.B).	0.040	%
1.2 Propyleneglycol	ad 100.0	%
Ampules 2 cc.		

Cysteine hydrochloride

1.2 pure cysteine dissolved in 25 ltrs. 203 % H_2SO_4 and subjected to electrolysis for 6-7 hours at 60-70 Amp., and 4.5 Volts. Heat and neutralize with $Ba(OH)_2$ to pH 6.9. After filtering pour into 4-5 % Cl and filter immediately. Evaporate and leave standing for crystallization. Filter by suction, wash with cold EtOH and dry.

Duodentrat

1 kg mucosae from small intestine, 0.2 kg mucosae from stomachs are hydrolyzed for 5-10 hours in 5 ltrs. 20% HCl. Dilute with H_2O , filter and remove excess of HCl by repeated evap. in vacuo.

The concentrate is adjusted to a N concentration of 0.8 %.

Glucose 0.5 %
Benzylalcohol 2 %
H₂O 100 %
Ampules of 3 cc.

Diphenyhydantoin.

1) Benzoin:- Mix 50 kg. benzaldehyde in 125 ltrs. of denat. alcohol with 10 kg KCN in 25 ltrs. H₂O. Reflux for one hour. After cooling filter crystals off by suction and dry in vacuo. Yield 95 % The KCN-solution in EtOH is used in the next batch.

2) Benzil:- Heat the benzoin in an enamel kettle with the double quantity of conc. HNO₃ for 3-4 hours. Pour the product of reaction into an excess of cold water. Suck the crystals dry, wash with water and dry. Yield 90-95 %.

3) Diphenyl hydantoin:- Mix 20 kg. benzil and 10 kg. Urea with 300 ltrs. denat. EtOH and heat until dissolved. Let cool down and add a solution of 33 kg. KOH in 15 ltrs. H₂O. Boil for 2-3 hours and pour into much water. Filter the ppt. off and neutralize the filtrate with 20% acid. (It makes little difference which acid is used). The crude product is centrifuged and purified by reprecipitation. Yield 80%.

Euzynorm.

Grind 5.300 kg. of pig's stomach and stir with 5.000 ltrs H₂O and 196 ltrs. HCl slowly at 37 % C. Centrifuge and evaporate the fluid in vacuo to contain about 30 % dry matter.

Eubasine (Sulfapyridine)

Acetyl sulfanil chloride.

537 kg. chlorosulfonic acid (- 300 ltrs) are stirred with 123 kg. techn. acetanilide. The temperature rises; when it attains 60° keep it constant by cautious cooling. After finishing the addition of acetanilide, cool while stirring and leave standing for several hours. Then pour on chopped ice. Let the temperature increase to 50° and now add chlorosulfonic acid and ice to keep the

temperature at 50°. In this way a well filtrable product is obtained. The sulfochloride separated is filtered, washed free from acid, centrifuged as dry as possible and carefully dried. The sulfochloride must be water free and not smell of acid.

Trimethylamine (supplement solution)

Prepare a trimethylaminic-HCl solution to make up for losses. Mix 1.2 kg. technical NH_4Cl with 3.3 kg. paraformaldehyde and fill into a 10 ltr. flask. Usually twelve 10 ltr. flasks are filled together. The flasks are connected to a reflux condenser and heated in oil bath to 80-100 until melting begins. Then remove from oil bath. The mixture melts completely with strong gas development. It is important to remove from the oil bath in right time to prevent the reaction from becoming too violent. The condenser must work well. When the gas development is almost finished, pour the contents of all flasks into one copper pan and heat. The heating has to be adjusted, so that the gas development does not become too violent. When a temperature of 150-140° is obtained, keep at this temperature until nothing but steam bubbles appear in the liquid. A concentrated aqueous solution of trimethylamine-HCl is obtained.

Recovery of trimethylamine solution is benzene. The aqueous trimethylamine-HCl solution "L" from an Eubasine batch, as will be described, is mixed with 50 ltrs. of the supplement solution and mixed with 200 kg. 30 % Na OH, in a distillation apparatus, the recipient of which contains 170 kg. C_6H_6 . All condensers are well cooled, also the recipient, either with water or salt solution. After adding the NaOH to the evaporating pan, heat slowly to 80° to liberate the trimethylamine. About 275 ltrs. of a solution in C_6H_6 is obtained, containing in each 5 ltr. 1 kg. trimethylamine.

For yield it is important that the cooling brine has a temperature of - 10°. The distillation of the trimethylamine should be done at moderate speed.

Eubasine.

Aminopyridine is purified by distillation in vacuo. Batch of 100 kg. The first distillate of 10 kg. is collected separately and used in the following batch. The main fraction is 70 kg. The later run of 10 kg. also goes into the next batch. The residue is rejected.

Loss ca. 10 %. 60 kg. purified aminopyridine are given into a clean and dry distiller kettle. Add 220 ltrs. acetone and, while cooling, and stirring, 165 kg. of dry acetylsulfanilic chloride. After sealing the kettle, add with cooling at moderate speed 215-230 ltr. of trimethylamine solution in C₆H₆. Stir the mixture for 3-4 hours longer, and evaporate the acetone and benzene as completely as possible. Add water, continue stirring. By heating, an aqueous mixture of phenyl-acetone may be obtained.

After cooling neutralize the contents of the kettle exactly to pH 7, filter the acetyl eubasine off and wash. Evaporate the aqueous filtrate in vacuo and use as solution "L" mentioned above. The acetyleubasine is mixed with 1200 ltrs. 10% NaOH and heated to boiling. First distill off the C₆H₆ - acetone, still present, then add 3 kg. animal charcoal and boil for 1 hour at reflux. Cool while stirring and filter. Heat the filtrate to 60° and neutralize with HCl (stirring). Dry and grind. It is important for the yield that water be kept away during the condensation. All solvents and agents must be water free.

Eubasimum - Na for ampules

Mix 125 kg. Eubasimum with an aqueous solution of 35 kg. NaOH. Stir and, if necessary, add water until all is dissolved. Evaporate in vacuo to obtain a thick paste of crystals, cool and mix with 50 ltrs of EtOH. Mix well and filter. The residues which stick to the walls may be left to be gained in the following batch. The contents of the filter wash very carefully with EtOH until the excess of NaOH is removed. This is recognized when the material becomes colorless. The alcoholic filtrate is returned into the process. Yield 125 kg. Eubasimum-Sodium.

Hematoporphyrin Nencki

Pour slowly 15 ltrs. of blood into 39 ltrs. of acetic acid, containing 100 g. NaCl, at 100° and with constant stirring. The temperature must be kept constant within a few degrees. Finally let cool down to 50°, filter the hemin crystals off and dry them.

36 g. hemin are added to 900 cc HBr-acetic acid (sp. G. 1.42), quickly and shaken for 15 minutes. Keep standing for 5-7 hours until a clear solution obtained. Then pour into 5 ltrs. of H₂O filter, and keep standing for another three hours. Then ppt. the hematoporphyrin dry adding conc. NaOAc solution. After filtration dissolve

the wet ppt. in dil. NaOH, filter the Fe(OH)_3 off and reprecipitate with AcOH. The dihydrochloride is obtained crystals at room temperature over H_2SO_4 .

Patent Application for Hematoporphyrin:- Under N 46654 IV c/12p. of November 29th, 1944, we applied for a patent at the German patent office, for manufacture of Hematoporphyrin, presenting the following claims:- 1) Method of preparing "ematoporphyrin, characterized as follows - Dry blood or blood parts are treated with H_2SO_4 in presence of HB or HCl or salts of same, at a temperature below 70° , preferably about 20° . The mixture is poured into 10 parts of water, and left standing until Hematoporphyrin is formed, the solution is separated from the residues and the hematoporphyrin is separated from the solution, purified and dried. 2) Method according to claim 1., characterized as follows - the Hematoporphyrin is absorbed from the solution by suitable absorbing agents, with a solvent, preferably aqueous alkali. From the solution it is pptd. with AcOH and mechanically septd., e.g. by suction, - purified and crystallized either free or as a metal complex salt.

Hepaventrat

5000 kg. minced liver with 4000 ltrs. H_2O and 400 kg. gastric juice are mixed with 230 kg. conc. HCl and dry start at 37° for 24 hours. Boil, filter and evaporate in vacuo to ca 70%, dry content. To make injectable material, dilute the extract with H_2O to 20% dryness and add alcohol to obtain 70% concentration. (This is alcohol % by weight, which is the usual German method of expressing alcoholic strength - A.E.M.). Keep standing for 14 days to precipitate the proteins completely, filter (AEM?) and evaporate again in vacuo to 20% dry substance. After a second filtration add absol. alcohol to obtain 90% alcoholic strength which precipitates the anti-anemic substances. Decant and wash repeatedly with absol. alcohol, suck dry and dry. The injectable preparation is adjusted to contain 7½% dry matter.

Hepatrat

Use the same process without the addition of gastric juice.

Mucin

Digest 205 kg. minced pig's stomachs with the same volume H_2O and a liter of HCl (Germ. Pharm. No.6) for 8 hours at 37° , boil shortly and centrifuge. Evaporate the solution in vacuo to 30% dry matter and precipitate with EtOH . Wash with alcohol until the

precipitate is free from hydrochloric acid, remove the EtOH and dry in vacuo.

Adrenal Cortex Extract

Digest the minced adrenals with 95% EtOH for 3-6 days with occasional stirring, filter and extract the residue three times more with 80% alcohol. Evaporate the combined extracts at 50-60° to 1/15 of their volume. Extract the residue with cold benzene in portions until the benzene is only slightly yellow in color. Evaporate the benzene solution at 45-50° and extract the residue twice with cold acetone.

Decant the acetone, evaporate at 45-50° and treat the residue with Petr. Ether and 70% EtOH. Shake the 70% EtOH-layer repeatedly with Petr. Ether. Then filter, to remove the last rests of adrenalin over zeolithe or permutite. Remove the EtOH by distl. and concentrate in vacuo.

Nucleotrat

Pancreas concentrate

Mix 300 kg. well minced pancreas with 600 l. H₂O and boil, while stirring for two hours. During that time adjust the pH to 2.5-5 with about 5 l. acetic acid. Then neutralize with 30% NaOH (a 10:1) and boil again for 1 hour. Filter hot through cloth bags and evaporate to $\frac{1}{2}$ volume. Keep at 32° and add Na₂SO₄ dry (300 g. per liter). Keep in ice box. After a few days remove the crystallized Na₂SO₄ by decanting the clear solution. Filter through hardened filter, evaporate, if necessary and filter again, until the depression of the melting point, as compared with a N content of 1%, is 1.5.

Omnival

A Vitamin A and D concentrate is bought from the firm Chemo-Dansk in Copenhagen. A quantity of 50% sugar syrup is added equivalent to the vitamin content of the liver oil. As a stabilizer of A and D equal quantities of oats- and liver extract were added. (Oats extract: 150 kg. of rolled oats is extracts with 90 liters of water and 300 liters of alcohol. The filtrate is evaporated in vacuo to extract consistency). The product is flavored with an extraction

of rose hips, which itself is a vitamin source. All manipulations were carried out with exclusion of air, i.e., in CO_2 atmosphere and the bottles were filled under CO_2 .

Elastonon, beta-phenylisopropyleamin, was purchased from Boehringer, Ingelheim.

Vitamin P.

Dilute 2 ltrs. of rose hips juice with 4 ltrs. of water and ppt. with 10 ltrs. of 10% lead acetate solution. Centrifuge and add to the clear liquid NH_3 until bromthymolblue is weakly blue, phenolphthalein not yet red. Centrifuge again and wash twice with water suspend the precipitate in 15 ltrs. of distilled water, add 25% HCl until Congo turns blue, methyl-organe weakly red. Pass H_2S through the liquid and filter the lead sulfide off. Evaporate the filtrate in vacuo and add an equal volume of abs. EtOH. Filter and add to the filtrate the 3 to 4 fold volume of alcohol. The dark plastic mass is centrifuged off and dried. Redissolve in water and add an equal volume of abs. alcohol. Now add a satd. soln. of $\text{Ba}(\text{OH})_2$ in 50% EtOH and centrifuge the red-brown ppt. off, suspend it in EtOH and pass CO_2 through the liquid. Filter and evaporate to dryness.

Patent Applications

Method of mfg. sulfanilaminopyrimidines. German. Data have been destroyed by bombing.

Claim: Method of preparing sulfanileminopyrimidines characterized as follows: - 6-halogenpyrimidines, having one or several hydrocarbon radicals attached to the pyrimidine nucleus are brought into reaction by melting with benzenesulfanamide compounds, having in para-position to the sulfonamide group a constituent that can be converted into the amino group. The melting is done with the addition of copper bronze as a catalyst and a waterfree basis that will bind the hydrochloric acid liberated. Finally the amino group in para position to the sulfonamide group is obtained in the usual manner.

Method of preparing hematoporphyrine. German 1943. Data destroyed by bombing.

The method is characterized as follows - dried blood or dried blood parts are treated with sulfuric acid in presence of HBr or HCl

or of salts of same at a temperature below 70°, optimally 20° (it is not clear whether this means 20° temperature or 20 below 70, namely 50°, A.E.M.). The product of reaction is poured into 10 volumes of water and left standing until the formation of hematoporphyrin is complete. After removal of the insoluble parts hematoporphyrin is obtained from the solution, purified and dried.

Second claim: (supplementing the first claim) - The hematoporphyrin is taken up from the solution by certain adsorbing agents such as Fuller's earth and is then eluted with aqueous alkali solution and precipitated with acid; i.e., acetic acid. It is separated by filtration with suction and crystallized either in free form or as a suitable salt, a metal complex compound or derivative.

Protein Foam, #2199. Data destroyed by bombing. Application 1945.

Method of preparing a fine voluminous stable protein "snow" by the action of hydrogen peroxide on blood containing catalase characterized as follows: The blood is mixed with 20 to 60 volumes of water and/or another protein containing fluid, and the hydrogen peroxide is added. Additional claim: before adding the hydrogen peroxide, the mixture is heated for a few minutes to 50°.

Method of making sulfanilamidopyrimidines. 24.13.1943.

1) The method is characterized as follows: 4-halogenpyrimidines, having one or several hydrocarbon radicals attached to the pyrimidine nucleus are brought into reaction with benzenesulfonamido compounds having in p-position to the sulfonamido group a substituent that can be converted into an amino group. This is done by melting the constituents together and obtaining later the amino group by the usual methods.

2) Supplement to claim 1. Copper bronce is added in the melting process as a catalyst and added a waterfree base is also to bind the free HCl formed.

Method of preparing stable compounds or vitamin K₃. 26.3.1944.

The method is characterized as follows: 1-hydroxy-2-methyl-4-aminophthalenhydrochloride is subjected to esterification of the phenolic hydroxyl group or amino group or to acetylation respectively. Subclaims: Method according to first claim consisting in acetylation of the hydroxyl or amino group or both. -- Method according to preceding claims consisting in partial saponification of the acyl group, e.g. the acetoxygroup, thus obtaining a half-acetyl compound.

Method of preparing pyridine mercury compounds. 27.4.1944.

1) The method is characterized as follows: A mercury salt of a lower fatty acid, soluble in pyridine, is heated at a reflux condenser with 10 mols of pyridine at common pressure. The excess or pyridine is distilled off and the residue is dissolved in water. Alkali is added and the precipitate removed. By adding the corresponding fatty acids the desired pyridine-mercury-fatty acid compound is obtained from the filtrate.

2) The pyridine-mercury-fatty acid compound is transformed into the pyridine-mercury halogen compound by adding aqueous inorganic halogen salts.

Method of flocculating protein containing emulsions. 5.6.1944.

1) The method is characterized by the combined use of pepsin or rennin with an iron or a heavy metal such as Fe.

2) Besides pepsin, rennin and heavy metal add an organic acid containing bound hydrochloric acid.

3) The organic acid containing HCl is glutaminic acid hydrochloride and the pH is adjusted to approximately 5.5.

Method of preparing blood anticoagulants.

1) Alginic acid first transformed into an ester with sulfuric acid.

2) Supplementing claim 1. chlorosulfonic acid is dissolved in pyridine and the alginic acid is added in small portions with cooling. Then the mixture is heated for several hours to 100° avoiding moisture.

3) Supplementing 1 and 2: The precipitated ester is suspended in water and by neutralization with alkali the alkali salt of the alginic acid sulfate is obtained.

Preparation of 4,6-(Disulfanilamino)-pyrimidines. 29.11.1944.

One mol. of a 4,6-dinalogenpyrimidine is condensed with 2 mols of a benzenesulfonamide, containing in para position to the sulfonamido-group a substituent that can be transformed into the amino groups. The condensation is done by melting the components with a base and copper powder. Then the amino group is obtained in the usual manner.

Foreign Patents Pending.

Sweden 2179/3000/42 1943. Method of preparing 4-sulfanilamido-pyrimidine in which the H atoms of the pyrimidine ring are partially or completely substituted by alkyl groups.

Description according to German applications. The base is specified as trimethylamine dissolved in benzene.

Switzerland 2180/74760 1943

Preparation of 4-)sulfanilamido-5-methyl-2,6-diethylpyrimidine. Description similar to German application. The 4-sulfanilamido-5-methyl-2,6-diethylpyrimidine forms colorless crystals m 192°, it is insoluble in acid and the usual organic solvents, easily soluble in aqueous mineral acids and aqueous solutions of strong alkalies.

Holland 2191/109208 1943

Blood protein - see description in scientific reports on treatment with ozone.

Bulgaria 4012/June 1944 - addition to 5160(5109)

Preparations of sulfanilaminopyrimidines.

Denmark 4013 Addition to 1781/42, July 6, 1944. Sulfanilamidopyrimidines.

France 4014/41791 Addition to 886009, July 24, 1944 - same subject.

Norway 4016/80-234 Addition to 74491, July 6, 1944 - same subject.

Portugal 4017 Addition to 21451, June 14, 1944 - same subject.

Serbia 4018 Addition to (5793) P371/44/3080, August 16, 1944 - same.

Spain 4019 Addition to 158411, July 14, 1944 - same subject

Turkey 4022 Application 4364, July 14, 1944 - same subject

Switzerland 4025 Addition to 74760 4(Sulfanilamido) 2-n-propyl-6-methyl-pyrimidine.

Serbia 2183.5793 Oct. 7, 1942 - sulfanilamidopyridines.

Slovakia 4026/P-9108-1-44 Sept. 25, 1944 - sulfanilaminopyrimidines

Switzerland 4029/97-448 Nov. 1, 1944 - 4-sulfanilamido-2-n-propyl-6-methyl-pyrimidine
4043, - 4-sulfanilamido-5-methyl-2,6-diethylpyrimidines.

Sweden 4052-1789/54, March 5, 1945 - stable compounds of Vitamin K₅
4036/1790-45, March 5, 1945 - preparation of pyridine-mercury compounds
4040/2004/45, March 10, 1945 - flocculation of protein containing emulsions.

Portugal 4051 March 15, 1945 - anticoagulant algin compounds.

Patents Held.

Germany	629,449	2.12.1933	Gland preparations
	492,281	3. 6.1927	Vitamin solution
	642,955	30. 1.1927	Pukling of foods
	697.262	22.10.1937	Vitamin A - enrichment
	706,695	9. 6.1938	Water soluble compounds of sulfanilamide.
	740,290	4. 3.1942	Protein from blood
	74 055	3. 4.1942	Protein from blood
	749.794	28. 5.1939	Preparation of sulfanilic acid amidopyridine (sulfapyridine)
Austria	146693	25. 7.1936	Blood transfusion tube
Belgium	448644	27. 2.1943	Albumin from blood
Bulgaria	5160	10.11.1942	Preparation of sulfanilamido
Denmark	63917	4. 2.1943	Protein from blood
France	731991	6. 6.1932	Salt mixture
	886009	15. 6.1943	Sulfanilamido-pyrimidines
	893235	14. 1.1944	Albumin from blood
Great Britain	388513	2. 3.1933	Improvements in and relating to the treatment of organic materials of cellular character with salts solutions and salt mixtures for use in such treatment.

Italy	337179	27. 2.1942	Protein from blood
Portugal	21431	21. 8.1942	Sulfanilamido-pyrimidines
Roumania	34420	16.12.1942	4-(sulfanilamido)-5-methyl- 2,6-diethylpyrimidine
Sweden	108926	2.11.1943	Protein from blood
Switzerland	221740	15. 6.1942	Sulfa compounds
Spain	158411	27. 8.1942	Sulfanilamido-pyrimidines
United States	1998179 2,031243	16. 4.1935 15. 2.1936	Salt mixture Treatment of organic cellular materials.

List of Reprints submitted by this Company.

1. C. Hegler: Behandlung der akuten lobären pneumonie mit $\text{^{133}I}$ ubasium. bericht über 202 Fälle, Deutsche Medizinische Wochenschrift, No.11.p,281 (1940)
2. Dr. Jules de Canniere: Neue Ergebaisse der Eubasiumbehandlung bei Pneumonie im Kindesalter, Münchener Medizinischen Wochenschrift, No.37.p,1015 (1941)
3. Dr. Müllnerfled : Die Bedeutung des Hämato porphyrin-Nencki)photodyn für die Therapie, Fortschritte Der Therapie, No.5.p,160 (1941)
4. W. Schober und S. Tappeiner: Gonorrhoebehandlung mit $\text{^{133}I}$ ubasimum, München er Medizinischen Wochenschrift, No.52. p,1440 (1940)
5. A. Hanerneck: Erfolgreiche Behandlung der $\text{^{131}I}$ otogenen Meningitis mit $\text{^{133}I}$ ubasium und Liquor-ausblasungen nach Zeller, Der Hals-Nasen-und Ohrenarzt, I.teil: Onginale 32, part 2/3 (1942)

6. H. Brieger: Die Wirkung von Eubasium auf die Ruhr im Säuglings- und Kindesalter, Kinderärztliche Praxis No. 5. 1943, p. 43.

7. Die Behandlung der "melancholien und endogenen Verstimmungs-zustände mit Photodyn. Printed by Nordmark and contains a series of abstracts of the literature on this subject from 1932-1937.

6. Dr. Christian Brennengräber, Chemische Fabrik und Co., m.b.H.
Lübeck

H. von Vultejus was interviewed at the office (Beckergrube 40) and R. Spangenberg, chemist, at the plant.

This firm belongs to the Possehl-Konzern. The holding firm has the name of L. Possehl and Co., of Lubeck and has a normal capital of 6 million marks. This holding company consists of 36 firms which produce the following products: Wool, fuel and lubricating oils, pig iron, steel and iron works, sanitary articles, minerals, raw material for welding, electrodes, mica and asbestos, shipping salt, technical and pharmaceutical chemicals, cellulose, metals, agricultural machines, fish preserves, and building materials.

The capital of this one firm is 350.000 marks plus 1 million which is invested by the holding firm.

The directors are: Heinz von Vultejus
Konsul Hans Kroeger

The chemists are: Richard Spangenberg
Dr. Theodor Bücher

The number of employees are:

Technical	36
Commercial	17

The pharmaceutical products were originally made at Schwaan at Rostock, but that is now in territory occupied by Soviet troops. The Lubeck plant originally made medical products in the field of food such as calcium and magnesium lactates, products cultures for milk and cheese, baking powders, and emulsions, as well as cleaning agents, disinfectants, and products for pest control.

At the request of the British Military Government they have transformed the Lubeck plant to produce the products originally made at Schwaan, and also the manufacture of insulin.

The real estate of the Lubeck firm comprises 16,954 sq m. of which 1989 sq m. are occupied by buildings. After the occupation of Lubeck by the British troops, foreign workers damaged the factory and destroyed some machinery and laboratory equipment. With the aid of the British Military Government, the buildings are being restored, and the equipment also to a large extent, so that limited production of insulin should begin in a short while.

Previously the Schwaan plant produced 10 million units of insulin per month. The Lubeck plant hopes to produce 3 million units per month.

Manufacturing Processes.

Peptone: The peptone is prepared from the insulin residues which are adjusted to pH 3 with oxalic acid and treated with whole hog's stomach. The oxalic acid is removed with calcium carbonate and the peptone solution is filtered off; stirred with much air and dried.

Insulin: Insulin is prepared by extraction with alcohol to give a concentration of 60% acidified to pH 3.8 with hydrochloric acid. Extraction proceeds for 4 hours at room temperature and the extract is separated by centrifuging. The residue is re-extracted with 60% alcohol at pH 3.8. The mixed liquids are readjusted to pH 3.8 if necessary and neutralized to pH 7 with sodium hydroxide. The product is centrifuged again and the liquid evaporated under reduced pressure below 25°C until all alcohol has been removed. The residue is diluted four or five times with water, adjusted to pH 3.8 with hydrochloric acid and filtered. The insulin hydrochloride is then salted out with saturated solution of sodium chloride.

Product is 1st CRUDE INSULIN HYDROCHLORIDE.

This is dissolved in 90% alcohol and reprecipitated at the iso-electric point. The precipitate is collected and dried with alcohol and ether. Product is 2nd CRUDE INSULIN HYDROCHLORIDE.

PURIFICATION: Second crude insulin hydrochloride is dissolved in 10 volumes of water with hydrochloric acid sufficient to give 10% of HCl then neutralized with caustic soda to pH 4.5, the precipitated insulin is filtered off and redissolved in water with HCl and again precipitated at pH 5.2. The precipitate is separated by centrifuging and dried with alcohol and ether. The dried material is dissolved in water with just a trace of hydrochloric acid and more hydrochloric acid added until the insulin precipitates. The settled precipitate from which the supernatant liquor is decanted, is again dissolved in water and caustic soda solution added to give pH 6.0. The insulin first precipitates and then redissolves. The solution is filtered and acidified to pH 5.4 and the precipitated insulin centrifuged out. The insulin is then dissolved in sufficient alcohol to give a concentration of 70% w/wC₂H₅OH, and the whole stirred to promote solution. The solution is filtered and the residue re-extracted with 70% alcohol twice and the solutions bulked. To the bulked product is added sufficient alcohol to give 90% C₂H₅OH, which precipitates the insulin. The insulin is separated by centrifuging, dried with alcohol and ether and finally vacuum dried. The product is "pure amorphous insulin"

The insulin is filled into vials under conditions far inferior to those acceptable in the United States and United Kingdom and is "sterilized", after filling, by heating in the final containers for 5 minutes at 100°C in the presence of 0.15% Nipagin (ethyl p-hydroxybenzoate) with which it is preserved.

The protamine used to make Zn.-protamine-insulin is obtained from Denmark.

Pancreatin:

The glands not suitable for insulin manufacture are dried in a vacuum oven at 40°C, mixed with sand, defatted with ether and acetone and ground to a powder.

Pepsin:

The mucosae from the stomachs of pigs are mixed with 4-5 fold quantity of water and adjusted to pH 3 with HCl. The liquid is mixed with some rice bran and pressed out. The clear filtrate is then saturated with NaCl. The pepsin is precipitated with skim milk and filtered off. The precipitate is held at 40°C for 48 hours and then the undigested part is filtered off. The pepsin solution is carefully filtered under vacuum and dried in vacuo.

Posterior Pituitary Hormones: The pituitaries are dried with acetone after first separating the anterior and posterior lobes. The posterior lobes are repeatedly extracted with acetic acid at 100°C and the combined extracts are salted out. The precipitate thus obtained is dissolved in water weakly acidified with acetic acid. This solution is treated with activated charcoal and stored for some time, after which the carbon is filtered off and eluted with phenol. The phenol solution is mixed with alcohol and ether which precipitates the preparation. The product thus obtained is tested on the guinea pig uterus.

Hay Fever Toxins: They obtained the original solution necessary for manufacture from Professor Kamann of the Botanical Institute of Hamburg. It contains a variety of pollens. This mother solution is mixed with physiological salt solution and preserved with phenol.

This firm does not have any patents. In view of the fact that it is the only insulin plant in the Hamburg area, it should be encouraged to produce as much insulin as possible.

7. Bengen & Co., Hannover.

This plant is largely destroyed, the remaining portion now being used for storage purposes. Formerly this company made veterinary products for the German army, and had a rather complete list of preparations. At present no production is being carried on at this

plant. Some work is being carried out at Hameln, Wahrberger Str.18. under the direction of Dr. Koch.

8. Riedel-de Haen A.G., Seelze Plant, Seelze b/Hannover.

Director Eberhard Bopp of the Seelze works was interviewed and the submission of a signed statement describing the history and present operations of the company was requested. Herr Bopp was very cooperative and willingly gave answers to all questions. Also present were Dr. Seemann and Dr. Hachmeister, factory managers at Seelze, who accompanied the team on a tour of the plant, explained the lay-out of the plant, and volunteered much information as to processes and products.

Historical Background of the Firm.

Riedel-de Haen A.G. was organized in 1928 as a result of the merger of the two parent companies; Riedel, A.G. of Berlin, founded in 1814, and, De Haen A.G. of Seelze b/Hannover, founded in 1861. In 1937 the Vanillinfabrik G.m.b.H. in Hamburg was formally merged with the company although the shares of this firm were acquired by Riedel-de Haen in 1928. (see Riedel-de Haen, Hamburg). The central offices and research laboratories of the firm are located in Berlin-Britz, Riedelstr 1-32.

Location of Plants and General Statement of Products of Each Establishment.

The manufacturing program of the individual plants may be qualitatively described as follows:-

Berlin-Britz: The manufacture of pharmaceutical specialties pharmaceutical chemicals such as, antipyrene, brom and iodo bismuth salts, vanillin and ethylvanillin.

List of pharmaceutical specialties described in "Remedia Riedel" and manufactured by Riedel-de Haen A.G., Berlin :-

Allotan - a mixture of desoxycholic acid and oil of garlic - each dragee contains the equivalent of 1g. fresh garlic.

Aperitol - a combination of acetyl-valeryl-phenolphthalein with equal parts of isovalerianic esters and the acetic esters of phenolphthalein.

Bismophanol - a 10% emulsion of the bismuth salt of phenylcinchoninic acid. The salt has a bismuth content of 26%.

Calcinol - Ampules of 10% and 20% concentration of calcium gluconate. Also in granular form for oral administration.

Carbo-Ormolon - A combination of 1 part medicinal carbon and 0.5 parts sodium 5-chloro-8-oxyquinoline sulfonate.

Catamin - A neutral ointment which contains as active ingredients 5% colloidal sulfur and 10% zinc oxide.

Ceadon - A combination of 0.05 g. extract of aloes and 0.1 g. desoxycholic acid.

Corodinin - An aqueous solution of sodium ethoxyquinoline-5-sulfonate with the addition of epinephrine HCl.

Decholin - Ampules and tablets of dehydrocholic acid or the sodium salt.

Decholin forte - A combination of dehydrocholic and desoxycholic acids.

Degalol - Peppermint oil and desoxycholic acid

Dijodyl - Ricinoleic acid diiodide having an iodine content of 46% - $\text{CH}_3(\text{CH}_2)_5 \text{CHOH} \text{CH}_2 \text{CI}-(\text{CH}_2)_7 \text{COOH}$

Dodonol - A mixture of B-bromallyl-sec.butyl barbituric acid and dimethylaminophenazone with desoxycholic acid combined in the ratio of 0.14: 0.11 g; 0.05 g.

Doralgin - A double compound of B-bromallyl-sec.butyl barbituric acid and dimethyl-amido-phenyl-dimethylpyrazolon.

Funareon - Sodium B-bromallyl-isopropyl-N-methyl barbiturate.

Gonosan - A solution of Kawa-Kawa gum and sandalwood oil

Hexal - A combination of sulfosalicylic acid 61% and hexamethylene-tetramine 39%

Jerolin - A liver oil emulsion containing 40% liver oil.

Jodarin - A 27.5% solution of methyl-triethanol ammonium iodide.
(C₇H₁₈O₃NI) in ampules

Lecitamin-C - A combination of lecithin, rose hips and dextrose.

Lecitamin - A lecithin preparation

Morpional - Pyrethrum solution

Neobornual - Isovalerylglycolic acid ester of borneol

Neoheral - See Hexal

Noctal - B-bromallyl-isopropyl barbituric acid

Olbisol - Bismuth salt of several substituted caproic acids in oil solution. Each cc. contains 0.04 g. bismuth.

Olobintin - A 10% solution of rectified, acid free oil of turpentine.

Olobintin "strong" - A 40% solution of the above

Pernocton - Ampules of 10% solution of sodium B-bromallyl sec.butyl barbiturate. Also tablets - Pernocton oral.

Physostol - A sterile 10% solution of Physostigmine in pure olive oil, absolutely water free.

Rectidon - Sodium B-bromallyl sec. amyl barbiturate as a stable 10% solution and cones

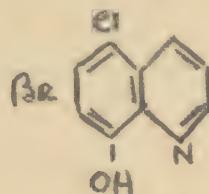
Rectidon compositum - A mixture of Rectidon 0.4 dimethylaminophenazon 0.15, Papaverine 0.03 and Ext. belladonna 0.02

Rinarom - A mixture of 12 parts ether, 2 parts ethyl chloride and 1 part chloroform with aromatics.

Salipyrin - phenyldimethylpyrazolon salicylate.

Tetrophan - Dihydronaphthacridin-mesocarbonic acid.

Vulnalin - Chlorbromoxyquinoline



M. P. 185°C

Ridle-de Haën also sell anesthetic ether, antipyrene, sterile gelatine, Gitapurin (digitalis), Idrabaryum ($Ba SO_4$). Idragin (acetyl salicylic acid) and Caffeine, "ecithin, Mergal (antiluetic), dextrose and yohimbine.

Seelze b/Hannover - Sulfuric acid, hydrofluoric acid and fluorides, inorganic chemicals for technical use, ether, laboratory reagents, chemicals for pharmaceutical use (corresponding to pharmacopeia requirements), colloidal graphite and plant preservatives.

Hamburg - Pharmaceutical chemicals, ethereal oils and perfums.

Organization of the Firm

Directors, Executive Committee

Dr. Friedrich Boedecker

Berlin-Dahlem, Thielallee

Dr. Eberhard Bopp

Seelze b/Hannover

Dr. Otto Dornseiff

Berlin-Schmargendorf, Sulzaerstr. 5

Divisional Directors.

1) Berlin -

Manufacturing: Dr. Grohmann
Dr. Reverey

Research Division: Dr. Heymons
Dr. Bruger
Dr. Ludwig
Dr Folk

Pharmaceutical Division: Dr. Kosidowsky

Sales: Herr Kröhne
Herr Güldenpfeinig

Purchasing: Herr Pufleb

2) Seelze b/Hannover

Manufacturing: Dr. Hachmeister
Dr. Seemann

3) Hamburg

Commercial: Hans Dieckmann
Manufacturing: Dr. Faetings

Number of employees at Seelze as of 1 February 1945.

Office workers, etc	163
Factory workers	804

Pharmaceutical chemicals of Pharmacopeia quality manufactured at Seelze and the production figures for 1944 are shown in the following list:-

	<u>Production 1944</u>	<u>kg.</u>
Acid.acetic.anhydric.pur.DAB 6	80.-	
Carbolic.liquefact DAB 6	1 030.-	
Formic.pur. 1.062 DAB 6	490.-	
hydrobromic 1,224 Ph.Ned	50.-	
hydrocyanic.pur. (2%) D. Ap.V.5	20.-	
malonic	30.-	
monochloracetic.pur.cr.D.Ap.V.5	380.-	
oxalic.pss.cr. Erg.B. 6	6 230.-	
sebaccinic.cr.	-	
succinic.pss.cr.Ergb.B.6	230.-	
sulfocresylic.pur.	-	
" crude.conc.	-	
sulfophenylic.para tech.	490.-	
trichloracetic.pur.cr.DAB 6	1 450.-	
Aether bromat.pss.DAB 6	1 120.-	
" dep.	440.-	
jodat. (Jodaethyl) D.Ap.V.5	300.-	
nitros.ver. (15%)	10.-	
pur.DAB 6	87 610.-	
sulfuric.pss. Ub.Natr. dest.	4 650.-	
Allylum bromat.	-	
Alumen kalic.pss.cr. DAB 6	-	
Alumin.chloric.piq. 30° Be	-	
sulfuric.pss.u. pur. Ph.Dan. u. DAB 6	6 370.-	
Ammon.acetic.liq. DAB 6	20.-	
benzoic.pss.cr.	110.-	
chlorat pss.cr.	14 360.-	
" ferrat. Erg. B. 6	-	
nitric.p.a.cr.	4 480.-	
" pss.	3 060.-	
oxalic.pss.cr. Erg.B. 6	1 740.-	
phosphoric.neutr. pss.cr. Erg B.6	410.-	
rhodanat.pss.cr.	20.-	
salicylic.pss.cr.	-	
Amylium nitros.pur. DAB 6	100.-	
Arsenic.jodat.pur.cr. D.Ap.V. 5	-	
Bar.chlorat.pss.cr.	20 170.-	
nitric.pss.cr.	1 820.-	
oxydat.hydric.pss.cr.	140.-	
- Benzol.p.a.	5 810.-	
Bismut subnitric.pss.cr.	-	
Cal.carbonic.pss.cr.	2 070.-	
chlorat.pss.cr. DAB 6	17 370.-	
bromat.pss.Erg. B 6	-	

	<u>kg</u>
chlorat.pss.ciss.gra.	-
citric.pur.	2 410.-
fluorat.pss.	470.-
Calc.hypophosphoros.pss.cr.	8 030.-
phosphoric.pss.cr.	-
" tribasic.pss.	-
phospholactic.pss.	-
sulfocresylic.	370.-
Carboneum sulfurat. p.a.	900.-
tetrachlorat.	80.-
Collodium elastic. DAB 6	-
med. (4%) DAB 6	2 530.-
Cupr.Ammon. sulfuric.pss.cr.	-
Natr.citric.	-
acetic.cr.	-
sulfuric.pss.cr.	3 050.-
Dimethylamidoazobenzol.	30.-
Ferri-Ammon.sulfuric.pss.cr.	-
Ferro-Ammon.sulfuric.pss.cr.	-
Fer.Benzoic.	-
phosphoric.oxydul. Erg.B. 6	-
tartaric.oxydul.	-
Jod.chlorat.tri. D. Ap.V. 5	-
Kal.acetic.pss.Ph.s. 10	280.-
acetic.pur. Erg.B. 6	1 400.-
bicarbonic.pss.cr.	-
bichromic.pss.cr.	130.-
bisulfuric.pss.Ph.Ross.	570.-
chlorat.pss.cr.	-
chloric.pss.cr.	12 930.-
chromic.pss.cr.	170.-
citric.pur. Ph.Brit.	390.-
ferricyanat.pss.cr.	-
ferrocyanat.pss.cr.	330.-
hypophosphoros.pss.cr.	1 000.-
metabisulfuros.pss.cr.	-
nitric.pss.cr. und plv.	12 030.-
nitros.pur.fus.in bac. Erg. B. 6	-
oxalic.pss.cr.	680.-
rhodanat.pss.cr.	1 000.-
Liq.Alumin.actic.	-
" actic.tartaric.	-

Ferri sulfuric.oxydat.pur. 1.425	1	380.-	kg
Ammonii caust. spirit.Dzondii (0.810) D.Ap.V.4		-	
Kali arsenic. DAB 6		-	
Lith.benzoic.		900.-	
borocitric		-	
Bromat.Erg.B. 6		-	
chlorat.Erg.B. 6		-	
citric.Erg.B. 6		-	
salicylic.		640.-	
Magnes.chlorat.pss.cr.		130.-	
citric		-	
lactic		-	
phosphoric.pur.		730.-	
salicylic		-	
sulfuric.sicc.		-	
Mang.chlorat.pss.cr. Erg. B.6	4	490.-	
citric.pss.		130.-	
lactic. pur. Erg. B 6		220.-	
peroxydat.pss.		-	
sulfuric.pss.cr. Erg. B.6	2	310.-	
Methyl.silicic.		480.-	
Natr. acetic.pss.cr.		360.-	
arsenicic.pss.cr. Erg. B 3		-	
bisulfuros.pss.cicc.		-	
carbonic.pss.cr.		110	830.-
" pss.sicc.		8	580.-
" pss. U.S.P. monohydrat			-
" pss. anhydr.			-
chlorat.pss.cr.		-	
citric.neutr. Erg.B. 6	1	780.-	
" " U.S.P. 10		320.-	
fluroat.pss.cr.		-	
formicic.pur. F.U. 5		-	
hypophosphoros.cr.	3	970.-	
nitric.pes.cr.		980.-	
nitroprossic. Reagens DAB 6		190.-	
nitros.pss.cr. DAB 6	10	300.-	
nitros.pss. in bac. DAB 6		50.-	
phosphoric.sicc.pss.	11	080.-	
pyrophosphoric.pss.cr. Erg B 6		600.-	
sulfuric.pss.sicc.		-	
sulfures.cr.		-	
thiosulfuric.cr.		-	
tartaric.pss.cr. Erg. B. 6		-	
Oleum lini sulfurat. D.Ap.V. 5		-	

Plumbum acetic.cr.	-
carbonic.pes.DAB 6	-
jodat.	-
Nitric.pss.U.S.P. 10	-
Rubidium jodat.	-
Spiritus aether. chlorat. D.Ap.V. 5	-
" nitros.DAB 6	-
Stront.chlorat.pss.cr. Erg B. 6	-
lactic.God.france	-
Tuischrotöl 50%	-
75%	-
90%	-
Zinc.salicylic.	-
culfophenylie.cr. Erg. B. 6	-

The Seelze plant and equipment were to a considerable extent old and obsolete. It is the belief of the Seelze directors that the Berlin plant was destroyed, and they are therefore taking such steps as may be necessary to initiate the production of pharmaceutical specialties formerly made in Berlin. Director Bopp stated that technical records, including patents of the firm, are believed to be in safe keeping at Gewerkschaft Wöldendorf, Wöldendorf bei Schwarzenfeld, Oberplatz, in the custody of Herr Kocher.

Some years before the war the firm sold to the Japanese a process for the commercial production of hydrogen peroxide, but the same process was also purchased by the Buffalo Electro-Chemical Company (U.S.A.). During the early phase of the war, large quantities of chloracetophenone were turned out by the Seelze plant. "Artificial fog" material composed of zinc powder, granulated zinc. and a varying proportion of oxidizing agent according to the smoke desired were also made at Seelze. Of possible interest is the production of calcium phosphide for naval use.

Details of the manufacturing processes for some of the pharmaceutical specialties formerly made in Berlin were available at Seelze and were submitted to the investigating team as complete descriptions, but the records were not complete and the details of some processes are to be found only in specified patents.

Manufacturing Processes or Patent References.

Bismophanol-bismuth salt of phenylcinchoninic acid. The preparation of this salt, containing 26 per cent of Bismuth is described in D.R.P. 704,297 and 715,267, as well as U.S. Patent 2,220,638.

The preparation of 5-chlor-8-oxyquinoline-7-sulfonic acid is described in D.R.P. 552,920.

The sodium salt of 8-ethoxyquinoline-5-sulfonic acid, described in U.S. Patent 1,688,259, is prepared as follows:-

100 parts 8-ethoxyquinoline is mixed with stirring with 500 parts of 7.5 per cent sulfuric acid and hydride, where in the acid becomes heated. The homogeneous reaction mixture is allowed to stand for 3-4 hours and then poured into 2-3000 parts of water plus ice. On dilution with water the resulting sulfo acid crystallizes. It is then filtered and washed with water. The very pure precipitate is for the most part used without further purification. After several crystallizations from hot water the acid crystallizes in long yellow needles which lose water of crystallization on drying at 100°C. Yield 126 parts - 86%.

Preparation of Cholic Acid and Desoxycholic Acid.

a) Raw gall acid mixture:

400 kg fresh cattle bile are treated in an autoclave at a temperature of 130-135° C with 12% sodium hydroxide 40° Be for a period of 5 hours. The contents of the autoclave are cooled over night to about 70°C and transferred to a container where the solution is neutralized with about 2/3 of the calculated quantity of hydrochloric acid (for example, with about 35-40 kg). The solution is then filtered through a bag filter over night and diluted with an equal volume of water. After cooling by the addition of ice, add 15% hydrochloric acid, slowly stirring the mixture, until acid to Congo red. The precipitated gall acid mixture is washed repeatedly by decantation, placed in a filter bag and washed again. The mixture is allowed to drain overnight; at room temperature it becomes a hard solid mass which may be broken into small pieces with a wooden mallet. It is then transferred to enamel trays and dried in a current of warm air at a temperature of 50-55°C; at first the mass melts but after several days changes to a brittle fatty mass that may be easily pulverized. Drying requires about 10 days. Average yield 5%.

b) Separation of the Fatty Acids:

The pulverized, gall acid mixture is added in portions of 30 kg. to a five fold quantity of decahydronaphthalene (Dekalin) con-

tained in a heated vessel equipped with an agitator, and well stirred for a period of at least 3 hours at a temperature of 90-95°C. The suspension is then filtered by suction on a steam-heated iron filter and washed with 5 kg hot decahydronaphthalene. The residue while still hot is placed in a pan where it is allowed to cool overnight. The following day the same operation is repeated twice, the first time with a three-fold quantity of decahydronaphthalene and the second time with a two-fold quantity.

c) Cholic acid:

The fat free gall acid mixture is thoroughly stirred with about one third of its weight of alcohol (spiritus) and after standing overnight is filtered on two suction filters, whereby a large part of useless greases are removed. The residue is then digested with $1\frac{1}{2}$ times its weight of alcohol at 40°C with stirring for one hour and allowed to crystallize for two days (in the summer time the mixture is cooled). One then filters off the cholic acid on a suction filter and washes the residue with $\frac{1}{2}$ the previous quantity of ethanol. The crude cholic acid is digested again with the same amount of ethanol at 40°C and it is often necessary to repeat this operation a third time, until a technical cholic acid of melting point 194-195°C is obtained. The finished cholic acid is freed of sodium chloride by washing several times with water and then dried. Yield 2.2 to 2.3% of gall (including accumulated residues).

d) Decahydronaphthalene desoxy acid (desoxycholic acid technical)

The combined alcoholic filtrates from C, which contains almost all of the desoxycholic acid in the form of decahydronaphthalene desoxycholic acid, with a significant quantity of cholic acid, amorphous gall acids and fat, are reduced to one half the volume and left to crystallize for two days in tin containers (in the summer the liquid is cooled). The suspension is then filtered on a suction filter and washed with a little alcohol. The mother liquid is reduced to one half the volume. On standing for several days a second crop of impure crystals is obtained. The liquid remaining is then completely evaporated from the solid and the residue dissolved in potassium hydroxide solution and set aside. The collected residue from a month's operation are again treated as before in the autoclave at 130°, again defatted, and recrystallized from alcohol. The fatty residues obtained from this operation are valueless and are discarded. Yield of decahydronaphthalene desoxycholic acid 1.5 to 1.6% of the gall.

The decahydronaphthalene desoxycholic acid is dissolved in an excess of aqueous sodium hydroxide and steam distilled until all of the decahydronaphthalene is removed. The solution is then filtered, precipitated with hydrochloric acid and dried.

e) Acetic Acid - desoxycholic acid.

The crude desoxycholic acid is crystallized from $2\frac{1}{2}$ times its weight of 80% acetic acid with some decolorizing charcoal and yields about 40% of its weight as acetic acid-desoxycholic acid. The mother liquor is reduced to one half its volume by vacuum distillation and yields after long standing a second impure crop of crystals, and after further concentration to one half, a third crop which must be further purified by crystallization from 80% acetic acid.

The acetic acid dregs from a month's production are distilled in a vacuum until free of acetic acid and the residue dissolved in potassium hydroxide to which is added double the amount of 92% alcohol. It is then saponified in an autoclave for 3 to 4 hours at 120°C to free the coordination complex of acetic acid. The alcohol is then distilled off and the dilute solution of the gall acid mixture precipitated with hydrochloric acid. (Acetic acid mother liquor dried residue).

This material which contains appreciable amounts of desoxycholic acid and cholic acid is again defatted and the working procedure as outlined above repeated. The residue obtained from the mother liquor of this operation is without value and may be discarded.

The combined acetic acid-desoxycholic acid is obtained in the preceding operations is dissolved in sodium hydroxide and precipitated with hydrochloric acid to obtain desoxycholic acid. Yield 0.65% of the gall.

Process for Dehydrocholic Acid.

To a solution of 200 grams of dried and alcohol free cholic acid in 1.2 liters acetic acid add dropwise and with stirring, a solution of 200 grams of chromic acid in 500 cc. acetic acid. One regulates the addition of the chromic acid solution so that the temperature which rapidly rises to 40°C, does not exceed this level. After the addition of the chromic acid is complete, the mixture is stirred for one hour and poured into 7 l. of water. After standing for several hours the crystalline dehydrocholic acid separating out is filtered on a suction filter and washed with water. The

chromium containing dehydrocholic acid is mixed with 1.5 l. water, treated with 500 cc. 33% soda solution and heated on the water bath. The acid goes into solution, and to completely separate the chromium hydroxide the solution is allowed to remain on the water bath for several hours, then filtered and the dehydrocholic acid precipitated by the addition of 30% acetic acid. The acid is then filtered on a suction filter, washed with water and dried at 70-80°C. Yield 150-160 g. If the acid is not free of chromium the last operation is repeated. For complete purification the acid is crystallized from 8 times its weight of 80% alcohol; some pure material may also be obtained from the mother liquor, m.p. 238-240°C. The process for the preparation of keto-cholanic acid is described in D.R.P. 576,965 and in U.S. Patent 1,933,003.

Process for the preparation of Dijodyl.

To 55 parts of ricinoleic acid contained in a vessel is added 300 parts of acetic acid (75-80%). The mixture is treated at room temperature with 0.1 part of iron powder and then 40 parts of finely powdered iodine are introduced. Under continuous stirring the solution is slowly heated until a temperature of 40-45°C is reached, and this temperature is maintained until crystallization begins, then it is allowed to cool under slow stirring. The mass is allowed to stand overnight, filtered by suction, washed with 50 parts of 75-80% acetic acid, then triturated in a mortar with 100 parts of 75-80% acetic acid, filtered by suction and washed with 50 parts acetic acid. The product is somewhat colored; to remove the acetic acid the dijodyl is triturated with 100 parts water, filtered by suction, and the residue is treated with water containing a small quantity of SO_2 . Allow to stand for 1-2 hours, filter by suction, and wash with water until the filtrate is no longer acid. Dry in a vacuum. The moist dijodyl is recrystallized from double its weight of methyl alcohol. It is soluble at a temperature of 40°C. The warm methyl alcohol solution is filtered on a suction filter; after a short time white needles crystallize. Allow to stand overnight, filter with suction, wash with 50 parts methanol, dry first in air, then at 40°C. Yield 69 parts m.p. 68°C. Iodine Content 45.71%.

9. Chininfabrik Braunschweig' Buchler & Co., Braunschweig.

This plant originally consisted of 20 buildings covering 17,500 sq m. of land. About 60% of the buildings were destroyed by bombing. Reconstruction of these buildings has been started. This plant is mainly concerned with the extraction of alkaloids from natural sources. In addition some radium extraction from Czech ore has been carried out at this plant. This radium was prepared for luminescent paints.

Branch factories are located at Boersum 74, and Horney & Krause, Schoeppenstadt.

During the war cinchona bark was obtained from Bolivia via Russian and later from the Japanese by submarine (Javenese and Sumatra bark). Present stocks of "Totaquine salts" are 5000 kg. with a further 10,000 kg. potential as bark. This material is at present distributed at various points throughout Germany, but is now being collected by military order at the above address. This firm has no research or testing facilities; any work of this nature having previously been carried out in university laboratories, for example, Göttingen.

Dr. Buchler informed us that there are in Germany, in addition to his company, only two other firms manufacturing significant quantities of cinchona alkaloids. These are:-

- 1) Boehringer und Söhne of Mannheim-Waldorf, who are merged with Zimmer and Co., of Frankfurt a.m. These are large manufacturers.
- 2) Boehringer Sohn of Ingelheim, who manufacture on a smaller scale.

Buckler and Co., has a normal capitalization of 1.100.000 marks.

The total number of employees is 70.

Products manufactured are:- Quinine and salts, cinchonine, quinidine, cinchonidine, quinoidine, (antipor), quineacid, cocaine, strychnine, yohimbine, radium, uranium, and luminescent paints.

The yearly production of quinine sulfate was 60.000 kg.
Raw material, intermediates and accessories necessary for a yearly production of 60.000 g. quinine sulfate are:-

Benzene	54.000	kg
Calcium oxide	216.000	"
Sodium hydroxide	48.000	"
Technical sulfuric acid	90.000	"
Pure " "	1.200	"
Sodium carbonate anhydrous	30.000	"
Active carbon A I	18.000	"
Carboraffin	7.200	"
Tartaric acid or calcium tartrate	6.000	"
Calcium chloride	15.000	"
Barium chloride	12.000	"
Hydrochloric acid	100	"
Sodium chloride	12.000	"
Ammonia 25%	1.800	"
Barium bromide	800	"

General method of manufacture:

The bark is treated with $\text{Ca}(\text{OH})_2$ and then extracted with benzene. The extract is treated with H_2SO_4 to obtain quinine bisulfate. By recrystallization the pure quinine is obtained.

Patents still in effect: D.R.P. 714087 antipor
 D.R.P. 677958 radium cartridge.

10. Orbis-Werke, Brunswick (Braunschweig)

This plant is very small (1 room) and is of no importance.
It manufactures antihelminitics.

11. Dr. Hans Brückner and Dipl. Ing. Gotthard Schmolke.
Bortfeld, Braunschweig.

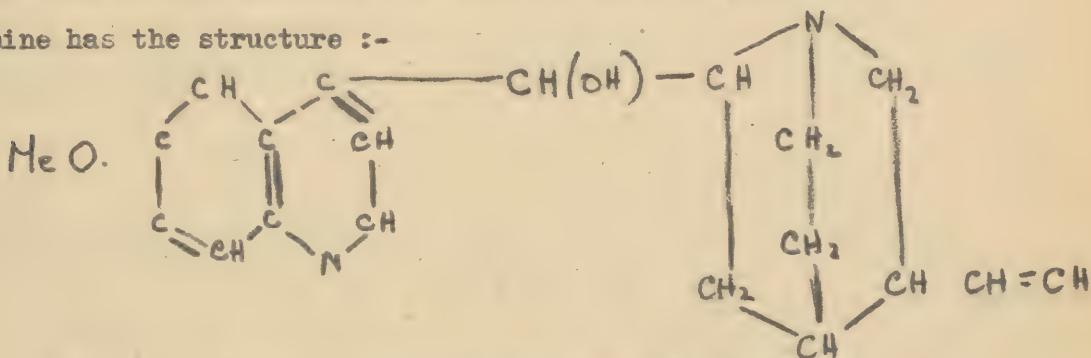
Dr. Hans Brückner and Dipl. Ing. Gotthard Schmolke, both originally of Breslau University Technische Hochschule, Department of Chemical Technology, now resident in Bortfeld near Brunswick. Interviews took place at the home of Dr. Ing. Kurt Fracke, Bortfeld 169. Dr. Fracke, a colleague of the above, was a lecturer in Physics and Engineering at Brunswick University and acted as interpreter.

Nature of Work.

Quinine-like Substances:

It transpired that Dr. Brückner and Herr Schmolke had prior to 1940 conducted private research work on the preparation of quinine-like substances, at Breslau University under the direction of the Head of Department of Chemical Technology, professor Ferber, who is now believed to be attached to the Department of Chemical Technology, Technische Hochschule, Munich. This work was considered to be of insufficient importance to be carried out under the auspices of the Reichsforschungsrat. Both Dr. Brückner and Herr Schmolke have been able to pursue this work since 1940 only in their spare time, Dr. Brückner having been directed by the Reichsforschungsrat to work on explosives at Kiel and Herr Schmolke at the Reichswehr.

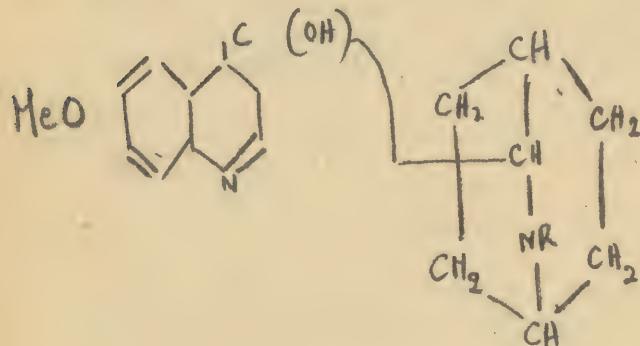
Quinine has the structure :-



It was hoped that by modification of the quinine molecule, substances would be achieved as would have quinine activity without

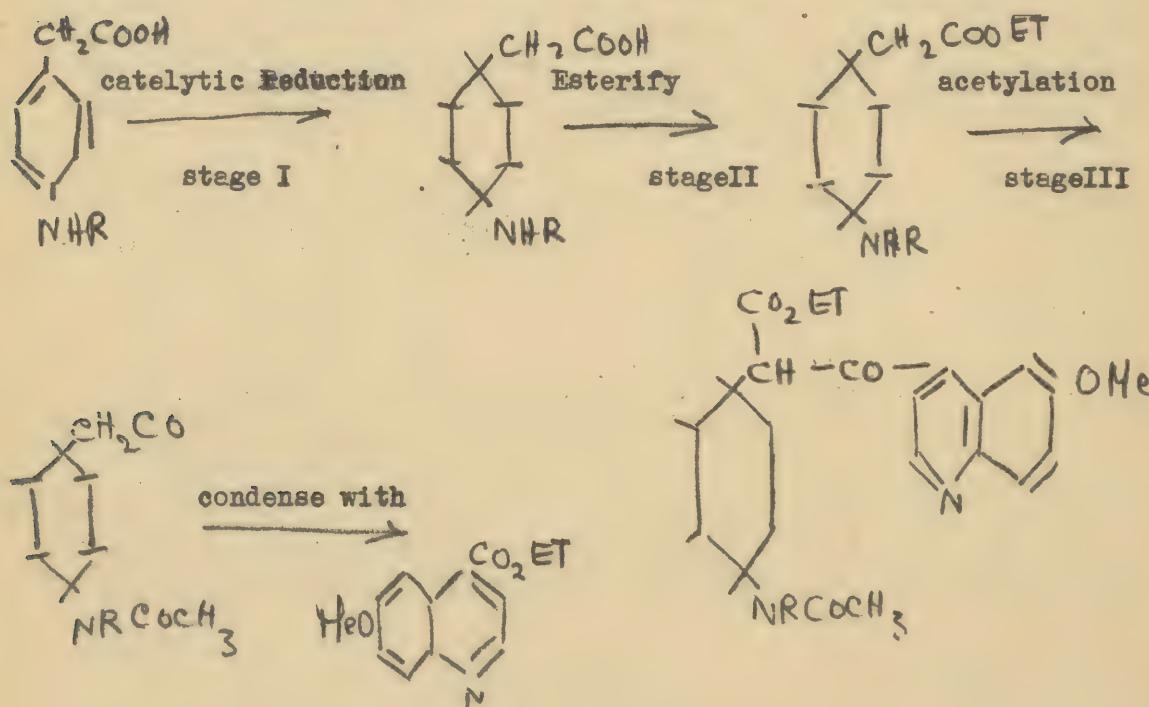
the well-known side-effects. It was further hoped that a compound might be produced that would be antagonistic to all types of malaria as contrasted with the action of atebrin and plasmoquin which are selective. There appears to be no theoretical or practical foundation for these views.

The type of compound ultimately envisaged is:-

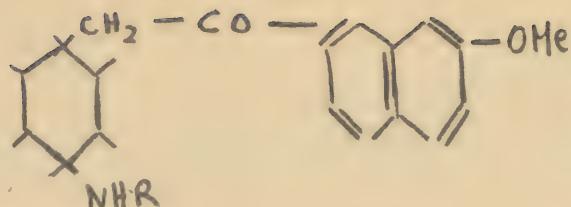


R-alkyl (particularly-CH₃) or H. Where R-alkyl the workers hope atropine like activity may be encountered(?)

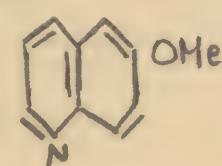
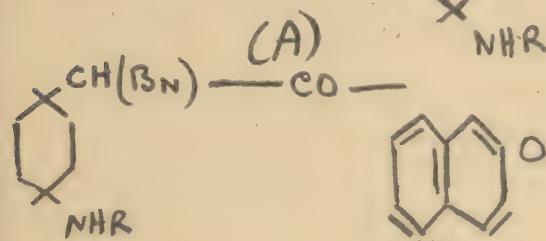
which it is intended to synthesize as follows:-



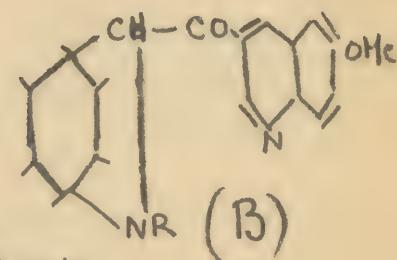
ACID hydrolysis
STAGE V



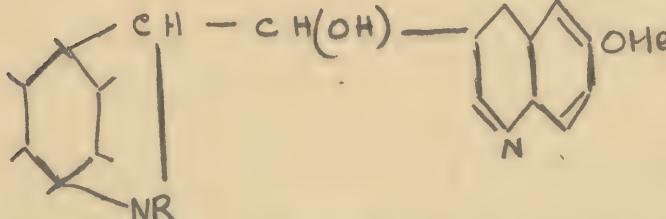
HalogenATION
STAGE VI



RING Closure
or per RABe



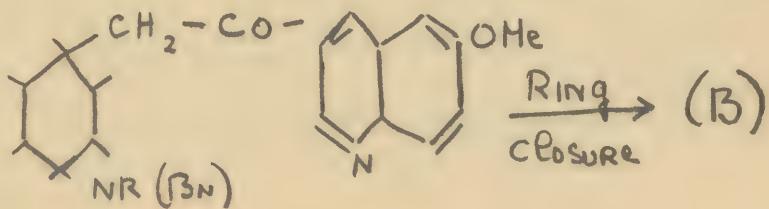
REDUCTION
STAGE VII



(B)

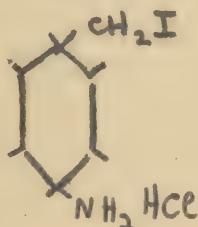
Alternatively it is proposed to proceed from (A) to (B) as follows:-
(Meisenheimer)

(A) N-Halogenation
with Na OBr



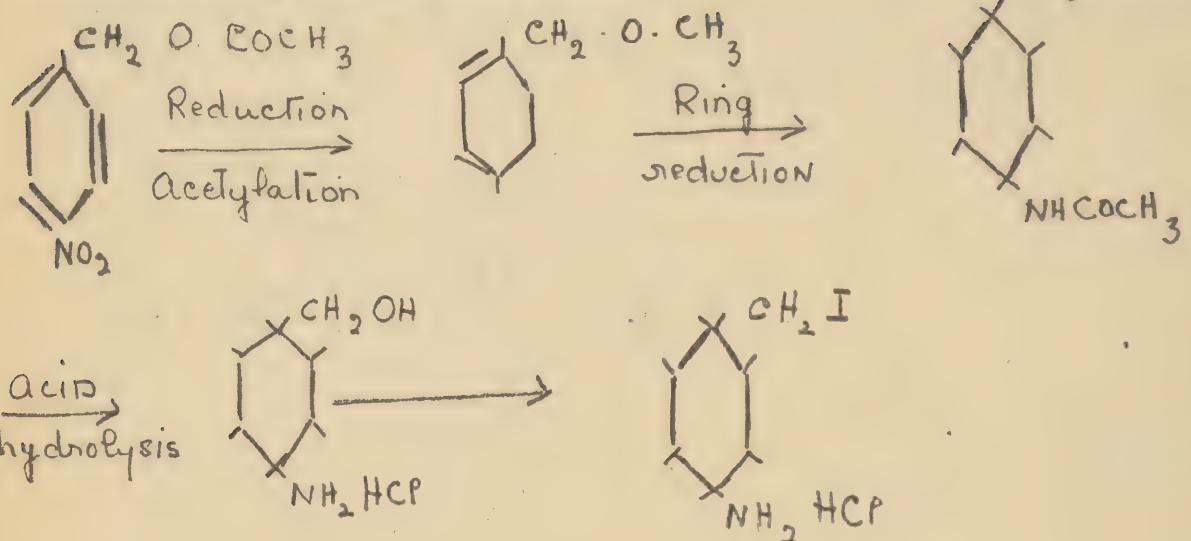
None of the above synthesis has been experimentally realized, but certain of the necessary reactions have been investigated by way of models. e.g.

1) As an extension of the work described by Ferber and Bruckner (Berichte - 1943 - 76 1019-1027 copy attached). It has now been shown by Dr. Bruckner (unpublished work) that a Rate type ring closure (ice Stage VII) may be brought about on the compound

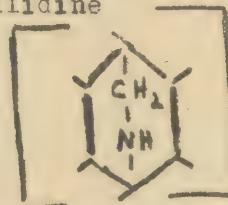


(4-aminocyclohexyl-methyl iodine),
this

substance having been prepared thus:-



2) By way of investigation the conditions necessary for bringing about the Claisen condensation in Stage IV, preliminary work (as yet unpublished) - see attached "Arbeitsbericht Dipl. Ing. G. Schmolke, 8.4.41., has been carried out. A copy of the paper (Berichte 72 \ 839-848, 1939) by Ferber and Bendix referred to in this "Arbeitsbericht", is also attached. Both isoquinuclidine



and

the corresponding N-methyl derivative have been tested pharmacologically on rats and guinea-pigs by Professor Eichler, Clinical Department of Breslau University (but Professor Eichler's present whereabouts unknown). It was found that neither of these substances had quinine-like activity and both were toxic. There was considerable possibility however, that one of the substances tested was not isoquinuclidine but was hexahydro-p-toluetine. N-methyl isoquinuclidine was prepared by a method similar to that described for quinuclidine by Ferber and Bruckner.

Further Remarks.

The work is in its very early stages and does not in our opinion merit further investigation.

It was brought to our notice that certain of the apparatus and chemicals, which to the pursuance of this work is in the possession of Dr. Rath, was thought to be in Einheim, near Heidelberg. These details were reported to Major Ignatieff, G (T) and C.W. 21st Army Group Main.

12. Organon N.V. Oss, Holland

Dr. M. Tausk, the scientific Director was interviewed. It was stated that this target had been completely examined last October by Colonel Phelps and Major Black of the British Army. Dr. Tausk stated that these men took written notes and obtained a complete written report of the work done under the direction of the Schering Co., during the occupation. A report by Colonel Phelps had been reviewed prior to departure of this team from London. The report, while well written, was incomplete in many technical details. It was assumed from Dr. Tausk's remarks that a second report had been prepared. This team has failed to find such report.

13. I.G. Farbenindustrie A.G., Institut zur Bekämpfung der Virusschweinepest (Behring Institute), Eystrup.

At present the staff consists of Professor Dr. Wilhelm Geiger, director of the Institute and two women technicians. During normal times annual production was as follows:-

Hog Cholera Serum	10.000 ltrs.
Hog Cholera Virus	200 "
Normal Bovine Serum	7.000 "

Dog Distemper Serum	500 ltrs.
Dog Distemper Virus	30 "

During the war some investigations of academic interest on the nature and epidemiology of these diseases has been done, but no new manufacturing procedures or methods of treatment or prevention have been developed. Dr. Geiger stated that research was greatly hampered by the war, and that the Nazi Government actually prohibited the treatment of hog cholera in Germany and decreed that all infected hogs should be killed.

12. Hamburger Serum Werke, G.m.b.H., Hamburg.

Dr. Wilhelm Weber is the director, and Herr E. Willis, assistant. The firm established 50 years ago. During the war it employed 25 persons, now 17 are employed. Only serum, antitoxins and vaccines are manufactured. It is housed in a converted residence. The equipment is old-fashioned, but in good condition. Facilities are media room, ampule and vial filling room, packaging department, sterilizing and glassware washing room, refrigerators, incubators and sterilizing equipment. Animals are housed in a separate building. There are accommodations for 30 horses (15 in use at present), and a small place for guinea pigs and mice. Chicken-egg incubators are contained in a separate warm room. Preparations and monthly production figures of each are:-

1.	Testserum (for blood grouping)	5 ltrs.
2.	Normalserum (human and animal)	10 "
3.	Rotlaufserum human (for erysipelas)	10 "
4.	Scharlachserum (scarlet fever serum)	10 "
5.	Tetanus-serum	110 "
6.	Diphtherie-Serum	100 "
7.	Diphtherie-Schutzimpstoff (vaccine)	10 "
8.	Fleckfieber-Schutzimpstoff (typhus vaccine)	3 "
9.	Rotlaufserum für Schweine (hog erysipelas)	100 "
10.	Coli-Serum	10 "
11.	Septikamie-Serum (influenza)	30 "
12.	Fohlenlahme-Serum (disease of colts)	20 "
13.	" -Vaccine " " "	10 "
14.	Rotlauf-Kulturen (streptococcus culture)	10 "

15.	Poliomyleitis-Serum	1 ltr.
16.	Typhoid vaccine	50 "

All of these preparations except the typhus vaccine and the scarlet fever anti-serum have been made for many years. All the preparations are made by standard methods. Method for typhus vaccine may be different. The blood of patients containing Rickettsia is passed through guinea pig brain, then inoculated by injection into eggs 6 days after fertilization. The eggs are incubated for 6 days, then the embryos and membranes are ground up and stored in phenol solution for 14 days. About 8% of the egg inoculations are successful.

Only standard methods which are well-known are used. No research is being carried out and there are no immediate prospects for new developments or techniques.

15. Schulke and Meyer A.G., Hamburg.

Personnel: Dr. Klessner - Director; Mr. Warnecke - assistant director; Professor Endres - Biochemist.

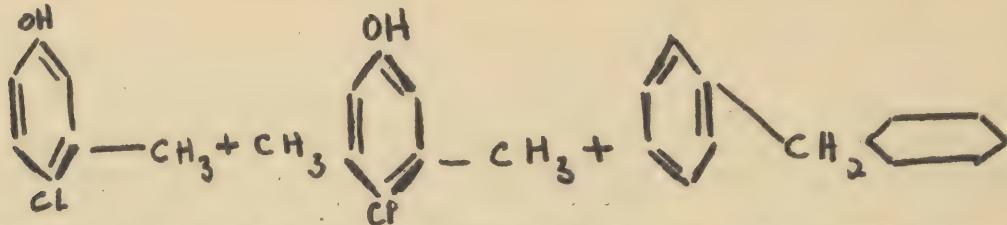
This is an old firm established over 50 years ago and employs 125 people, of whom 61 are office and laboratory employees. The rest are factory workmen.

The average monthly production of its chief products are:-

Lysol	40.000	kilos
Sagratan	100.000	"
Alka lysol	6.000	"
Quartamon	6.000	"
Kudan-tincture	2.000	"

The above are specialties of the house in the field of surgical and clinical antiseptics with the exception of lysol. The firm has product patents on Sagratan, Alka lysol and Quartamon. A process patent only is held on Kudan tincture.

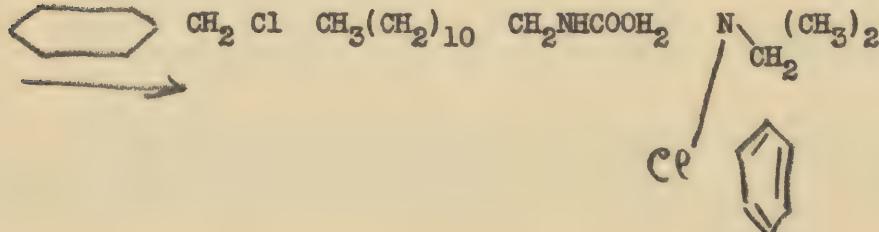
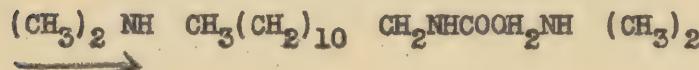
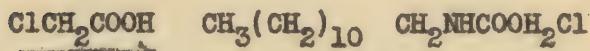
Sagratan is an old product, essentially a 12% solution of chlorinated cresols, Xylenol and benzyl phenol in an oil and soap medium



Advantages claimed for Sagratan are that it has higher antiseptic activity than lysol, it is odorless, non-irritating to skin, and less toxic than lysol.

Alkalopal is pure ortho-cresol in an excess of sodium hydroxide solution. The excess alkali is necessary to dissolve mucus in sputum so that tubercle bacilli are exposed. Soap 20% is added to prevent oxidation.

Quartamon available since 1938 is a quaternary ammonium compound 10% in water. It contains 1% sodium azide as a rust preventive since the preparation is designed for use in sterilizing surgical and dental instruments. The compound also contains some Na₃PO₄ and is adjusted to a pH of approximately 8. It is action active and is prepared as follows:-



Kudah Tincture. is a general surgical antiseptic for use primarily in disinfecting skin pre-operatively. It is designed to replace iodine tincture. It is an alcoholic solution of O-benzyl-p-chloro-phenol plus p-chloroxylenol plus quartamor. It is said to be less irritating, less toxic, and to cause less tissue damage than iodine.

Dr. Endres has developed a scabicide known as uoriphen. It is manufactured by Dr. Hammer & Co., G.m.b.H., at Arster Krug Chausee No 48, Hamburg. It contains 3.0 to 3.3% chlorinated phenan (sagratan) plus 6.0 to 6.5% soap plus 12% alcohol in aqueous solution. It is claimed to be superior to Mitigal. More than 2 million cases of scabies were treated with Moriphen by the Wehrmacht with great success. It is applied to the skin undiluted, avoiding mucous membranes and allowed to dry for 10 minutes. It may then be washed off. One application is said to kill both parasites and nits. Records of its use by the Wehrmacht were not available.

Samples of Moriphen, Sagratan and Quartamon were obtained and sent to Paris Headquarters through channels.

Appendix I. A Method for the Determination of Sontochin in Urine.

Methode zur Bestimmung von Sontochin im Harn.

Von W. Weise (Institut f. Schiffs- u. Tropenkrankheiten, Hamburg).

1. Prinzip der Methode.

Nachdem die Fluoreszenz des Sontochins in schwefelsaurer Lösung sich als ungeeignet zur Bestimmung kleiner Mengen erwiesen hatte, wurde ein brauchbares Prinzip für die quantitative Erfassung in der Trübung gefunden, die sehr verdünnte Sontochinlösungen nach Zusatz von Chinireagens liefern.

Das angewandte Reagens stellt eine essigsaurer Lösung von Kaliumquecksilberjodid dar von folgender Zusammensetzung:

10 g Kaliumquecksilberjodid
95 ccm dest. Wasser
5 ccm Eisessig.

Wäßrige und schwach saure Lösungen von Sontochin sind diesem Reagens gegenüber sehr empfindlich. Versetzt man 5 ccm einer wäßrigen Lösung, die 0.1 mg% enthält (1 : 1 000 000), mit einem Tropfen Reagens (dieses Verhältnis wurde immer gewahrt, also z.B. 2 Tropfen Reagens auf 10 ccm), so tritt sofort keine Veränderung auf, nach 5 Minuten ist aber eine ganz geringe Trübung wahrzunehmen. In verdünnter Schwefelsäure ist die Reaktion noch empfindlicher. So gibt eine Lösung der gleichen Konzentration in ~~Exzess~~ 0.2 n-Schwefelsäure zwar sofort auch keine Trübung, nach 5 Minuten ist diese aber viel deutlicher als im reinem Wasser. 0.2 mg% in 0.2 n-Schwefelsäure geben sofort einen Hauch, nach 5 Minuten eine deutliche Trübung, während in Wasser sofort nichts zu erkennen ist, nach 5 Minuten eine ganz geringe Trübung.

Trübungen lassen sich messen entweder durch Photometrie des seitlich abgebeugten Lichtes (Nephelometrie) oder durch Bestimmung der Absorption des durchfallenden Lichtes (Diaphanometrie). Wir entschieden uns für den zweiten Weg, obwohl die theoretischen Grundlagen hier weniger übersichtlich sind. So hat in diesem Falle das Lambertsehe Gesetz keine Gültigkeit, d.h. die Extinktion ist der Schichtdicke nicht proportional. Wenn aber einmal die Tabellen (bzw. Kurven) für die gangbaren Schichtdicken aufgestellt sind, ist die Bestimmung nicht umständlicher als mit der nephelometrischen Anordnung. Auch läßt sich die Messung mit der gleichen Ausrüstung des Pulfrich-Photometers durchführen, wie sie für kolorimetrische Bestimmungen notwendig sind.

Wie schon die qualitativen Vorversuche gezeigt hatten, dauert es einige Zeit, bis die Trübung nach Zusatz des Reagens ihr Maximum erreicht hat. Es mußte also geprüft werden, nach welcher Zeit dieser Vorgang so weit abgelaufen war, daß annähernd konstante Verhältnisse herrschten.

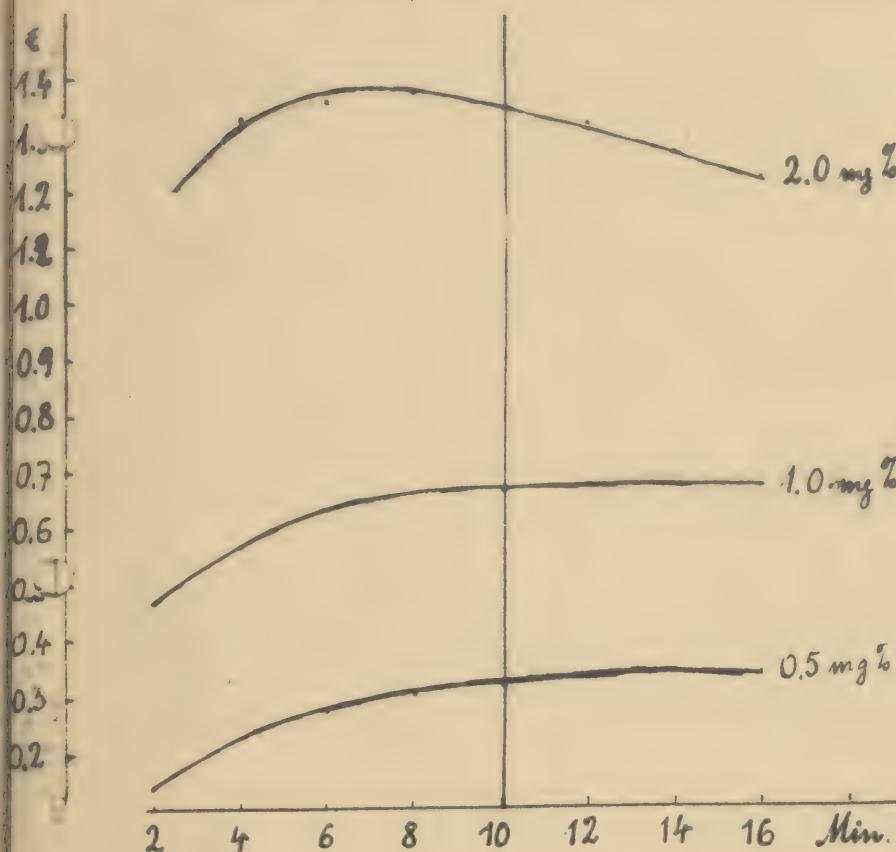
Es wurden dehalb Lösungen verschiedener Konzentration in Intervallen von ~~zu~~ je zwei Minuten gemessen und so die nachfolgenden Kurven gewonnen.

Die Kurven lassen erkennen, daß für kleine Konzentrationen das Maximum der Trübung nach etwa 15 Minuten erreicht ist; für mittlere ist schon nach 10-12 Minuten der Höchstand erreicht, der dann während der weiteren Beobachtungszeit erhalten blieb. Für höhere Konzentrationen treten die höchsten Extinktionen schon früher, etwa nach 8 Minuten, auf. Dann macht sich die eintretende Teilchenvergrößerung bemerkbar, so daß die Kurve dann langsam, aber stetig abfällt.

Auf Grund dieser Ergebnisse schien eine Wartezeit von 10 Minuten bis zur Ablesung am besten geeignet. Die Messung wurde immer so vorgenommen, daß genau 10 Minuten nach Zufügen des Reagens und Umschütteln die Ablesung begonnen wurde. Es wurden rasch zwei Messungen ausgeführt,

dann die Tröge umgewechselt und noch zweimal abgelesen.

Die für die grundlegenden Versuche zur Ausarbeitung der Methode und für Kontrolluntersuchungen benötigten verdünnten Sontochinslösungen wurden durch entsprechende Verdünnung von "Sontochinlösung 5%ig" in Ampullen hergestellt. Als Verdünnungsflüssigkeit diente 0.2 n-Schwefelsäure.



2. Bestimmung des Sontochins in reinen Lösungen.

Es war angesichts der mannigfachen Einflüsse, die für die Stärke von Trübungen maßgebend sind, zu erwarten, daß keine einfache Proportionalität zwischen der Größe der Extinktion und der Konzentration bestehen würde. Deshalb mußte zunächst eine Eichkurve aufgestellt werden. Aber auch eine solche Eichkurve hat ~~noch~~ nach dem oben Dargelegten nur Gültigkeit für eine bestimmte Schichtdicke. Es müssen also so viele Eichkurven ermittelt werden, als verschiedene Schichtdicken zur Anwendung kommen sollen. Im Verlaufe der Versuche ergab sich, daß man für die meisten Zwecke mit Schichtdicken von 0.5 und 1 cm auskommt. Für sehr kleine Konzentrationen ist es vorteilhaft mit 2 cm-Kvetten zu arbeiten. Es genügt aber hier die Festlegung für einen kleinen Bereich, in dem man in 1 cm Schichtdicke eine zu niedrige Extinktion erhalten würde.

Zu 10 ccm der angewandten Verdünnung in einem Reagensglase werden 2 Tropfen Reagens gegeben und gleichzeitig die Stoppuhr in Gang gesetzt. Bevor 10 Minuten abgelaufen sind, wird die Flüssigkeit in einen Trog gefüllt, für dessen Schichtdicke die Kurve aufgestellt werden soll. Auf der anderen Seite wird destilliertes Wasser gegengeschaltet. Nach Ablauf von genau 10 Minuten wird die Messung begonnen unter Vorschaltung des Filters S 61, das bei günstiger Lichtstärke eine genaue Einstellung erlaubt.

Die Festlegung der Kurvenpunkte geschah durch Mittelung aus mehreren Bestimmungen, die im allgemeinen gut übereinstimmten. So wurde für eine Konzentration von 2.0 mg% in 0.5 cm Schichtdicke nacheinander gemessen: 0.657 - 0.670 - 0.650 - 0.674. Die größte Abweichung vom Mittel (0.663) betrug also -0.013, entsprechend knapp 2% des Mittelwertes.

Bei diesen Versuchen ergab sich, daß unterhalb von 0.3 mg% die Streuung so groß wird, daß man diesen Bereich besser ausschaltet. Für die Bestimmung im Harn empfiehlt sich dies auch aus einem anderen, später zu erörternden Grunde. Oberhalb von 3.0 mg% werden auch in 0.5 cm Schichtdicke die Extinktionen so hoch, daß die Messung schwierig wird (die Handhabung von Küvetten geringerer Schichtdicke ist unbequem). Da höhere Konzentrationen jederzeit durch geeignete Verdünnung in den optimalen Meßbereich hineingezückt werden können, wurden die Eichkurven nur bis zu einer Höchstkonzentration von 2.5 mg% ermittelt.

Anstatt der ursprünglichen Eichkurven sind aus praktischen Gründen die mit ihrer Hilfe ermittelten Tabellen beigefügt, aus denen sich, wenn es gewünscht wird, die Kurven leicht wieder rekonstruieren lassen.

Für die Festlegung der Eichkurven wurden die Lösungen, wie erwähnt, aus Ampulleninhalt durch Verdünnung bereitet. Mit Hilfe von Sontochin-Tabletten gelang es nicht, beständige Lösungen herzustellen. Wurden die Tabletten fein zerrieben, mit 0.2 n-Schwefelsäure digeriert und dann filtriert, so trat später Trübung ein. Dagegen ergaben Tabletten von Sontochin R ein klar bleibendes Filtrat. Eine Verdünnung, die nach der Berechnung eine Konzentration von 1.0 mg% besitzen sollte, ergab bei der Bestimmung aber nur 0.875 mg%.

Da sich bei den Vorversuchen für Lösungen in 0.2 n-Schwefelsäure eine größere Empfindlichkeit der Reaktion ergeben hatte als für rein wässrige, war es notwendig nachzuprüfen, ob kleine Abweichungen in der Konzentration der Schwefelsäure von Einfluß auf das Ergebnis sind. Es wurden deshalb Lösungen gleicher mittlerer Konzentration in Schwefelsäure von verschiedener Normalität bereitet. Die Messungen ergaben:

Lösung in 0.1 n-Schwefelsäure:	E = 0.587
" " 0.2 n- ":	E = 0.581
" " 0.5 n- ":	E = 0.581.

Kleine Abweichungen in der Konzentration der Schwefelsäure sind also ohne Bedeutung.

Mit Rücksicht auf die besonderen Verhältnisse im Harn war es erwünscht für reine Lösungen zu ermitteln, in welcher Ausbeute die angewandte Menge niedergefunden wurde, wenn die Verarbeitung in derselben Weise vorgenommen wurde, wie dies bei der Bestimmung im Harn geschah. Die Analysen wurden demnach folgendermaßen vorgenommen:

200 ccm Lösung, in denen sich eine bekannte Menge Sontochin befand, wurden in Scheidetrichter mit 10 ccm 50%iger Kalilauge (60 g Stangenalkali auf 40 ccm Wasser) versetzt und zweimal mit je 200 ccm Aether ausgeschüttelt. Die vereinigten Atherauszüge wurden mit wenig Wasser gewaschen und dann das Sontochin mittels 0.2 n-Schwefelsäure dem Aether entzogen, zuerst mit 25 ccm und dann noch mit 15 ccm. Die abgetrennten sauren Auszüge wurden in einem genau graduierten 50 ccm-Zylinder mit Stopfen gesammelt und mit 0.2 n-Schwefelsäure auf ~~zu~~ 50 ccm aufgefüllt.

Die sauren Auszüge enthalten beträchtliche Mengen Aether gelöst, der die Trübungsreaktion durch Herabsetzung ihrer Empfindlichkeit erheblich beeinflußt. Um den Aether zu entfernen, werden die Auszüge in Porzellschalen auf dem Wasserbade während einiger Minuten erhitzt, bis keine feinen Blasen von verdampfendem Aether mehr aufsteigen. Nach Abkühlen wird in den Zylinder zurückgegossen, mit wenig Wasser nachgewaschen und auch mit Wasser das Volumen bis zur Marke ergänzt.

Vor Ablösung der Messung stellt man mit 5 ccm Lösung unter Zugeben eines Tropfen Reagens eine Vorprobe an. Bei einiger Erfahrung erkannt

man aus der Stärke der entstandenen Trübung, ob noch vorgängig eine Verdünnung vorgenommen werden muß. Mit dieser oder mit der ursprünglichen Lösung setzt man dann die Reaktion an, wie oben bei der Festlegung der Eichkurve beschrieben.

Die Ergebnisse von zwei Ausbeuteversuchen waren die folgenden:

1) Eine Lösung, die 5.0 mg Sontochin in 200 ccm 0.2 n-Schwefelsäure enthält, wurde nach Zusatz von Alkali dreimal mit je 200 ccm Äther ausgeschüttelt und die drei Extrakte getrennt für sich weiter verarbeitet, um die Wirksamkeit der Ausschüttungsmethode zu kontrollieren.

Extrakt I: Vor der Anstellung der Reaktion erwies sich eine weitere Verdünnung auf 500 ccm als zweckmäßig. Mit dieser wurde in 1 cm Schichtdicke die Extinktion 0.645 gemessen. Aus der Tabelle ergibt sich eine Konzentration von 0.96 mg%. In 500 ccm Extrakt waren also 4.80 mg enthalten. Somit wird mit dem ersten Ätherextrakt schon 96% des vorhandenen Atebrins entzogen.

Extrakt II: Mit dem Extrakt (50 ccm) erhält man eine Trübung, die in 2 cm Schichtdicke einer Extinktion von 0.022 entspricht. Dieser niedrige Wert lässt keine genaue Ermittlung der Konzentration zu. Jedenfalls enthält der zweite Ätherauszug nur noch ganz geringe Mengen Atebrin.

Extrakt III: Wie vorauszusehen betrug hier die Extinktion in 2 cm Schichtdicke nur 0.006, lag also innerhalb der Fehlergrenze.

Im ganzen kann man die Ausbeute bei diesem Versuch zu etwa 97% schätzen.

2) Eine Lösung von 1.0 mg Sontochin in 0.2 n-Schwefelsäure lieferte 50 ccm Extrakt, der für die direkte Bestimmung geeignet war. In 0.5 cm Schichtdicke wurde 0.646 gemessen. Aus der Tabelle ergibt sich eine Konzentration von 1.87 mg%. In 50 ccm Extrakt sind also 0.935 mg enthalten, so daß die Ausbeute 93.5% beträgt.

Die Ausbeuten bei der Isolierung von Sontochin aus reinen Lösungen nach dem angegebenen Verfahren sind also befriedigend.

Bestimmung des Sontochins im Harn.

Bei der Ausschüttung alkalischen Harns mit Äther kommt es leicht zur Bildung lösiger Emulsionen. Diese lassen sich fast immer vermeiden, wenn man den Harn möglichst frisch verarbeitet und das gleiche Volumen Äther anwendet, also z.B. auf 200 ccm Harn auch 200 ccm Äther. Der Ätherverbrauch ist bei diesem Vorgehen zwar ziemlich hoch. Man kann den benutzten Äther aber leicht wieder regenerieren, indem man einmal mit stark verdünnter Schwefelsäure und dann noch zweimal mit Wasser ausschüttelt. Wie sich gezeigt hat, kann man den so gereinigten Äther trotz seines Wassergehalts ohne weiteres wieder verwenden.

Eine Fehlerquelle für die Bestimmung des Sontochins im Harn beruht darauf, daß auch normale Härne, die frei von Sontochin, Atebrin oder Chinin sind, gelegentlich eine schwache Trübung geben, wenn man die Extrakte mit dem Reagens versetzt. Bei der Messung ergab sich für die spezifische Extinktion (E in 1 cm Schichtdicke) im Höchtfalle der Wert 0.06. Aus der Eichkurve ist die dieser geringen Extinktion entsprechende Sontochin Konzentration nicht mehr zu entnehmen; man kann sie zu etwa 0.2 mg% schätzen. Unter Berücksichtigung des Extraktvolumens (50 ccm) würden dadurch also etwa 0.1 mg Sontochin vortäuscht werden. Ob bei bestimmten Krankheiten die Stoffe, welche diese Trübung verursachen, in größerer Konzentration auftreten, bedarf noch einer eingehenden Prüfung. Bei Malariakranken überschritten sie das bezeichnete Maß nicht.

Um den Einfluß dieser "physiologischen Trübung" auf die Genauigkeit der Sontochinbestimmung im Harn zu untersuchen, wurden normale Härne mit verschiedener Mengen Sontochin versetzt und dann die Bestimmung durchgeführt. Die angehandten Normalhärne ergaben bei direkter Verar-

beitung keine Trübung.

1) 200 ccm Normalharn, mit 5.0 mg Sontochin versetzt, wurde, wie üblich, zweimal ausgeschüttelt, die beiden Ätherauszüge aber getrennt verarbeitet.

Extrakt I: Nach Verdünnung auf 250 ccm wurde in 0.5 cm Schichtdicke die Extinktion 0.656 gemessen. Aus der Tabelle ergibt sich die Konzentration 1.92 mg%; es sind also in 250 ccm Extrakt 4.80 mg Sontochin enthalten, so daß sich schon bei einer Ausschüttelung eine Ausbeute von 96% ergibt.

Extrakt II: In 2 cm Schichtdicke wurde gemessen $E = 0.042$. Der zweite Auszug enthält also nur noch Spuren von Sontochin.

2) 200 ccm Normalharn, mit 2.0 mg Sontochin versetzt. Es wurde zweimal mit Äther ausgeschüttelt, die Auszüge getrennt verarbeitet.

Extrakt I: Nach Verdünnung auf 100 ccm wurden in 0.5 cm Schichtdicke gemessen $E = 0.669$, wofür sich aus der Tabelle eine Konzentration von 1.98 mg% ergibt. In 100 ccm Extrakt sind also 1.98 mg enthalten.

Extrakt II: In 2 cm Schichtdicke wurden gemessen $E = 0.106$. Die Konzentration beträgt nach Schätzung 0.2 mg%. In 50 ccm Extrakt sind also etwa 0.1 mg enthalten.

Die Gesamtausbeute dieses Versuchs beträgt demnach 2.08 mg, entsprechend 104%.

3) 200 ccm Normalharn, mit 0.5 mg Sontochin versetzt, wurden zweimal ausgeschüttelt und die Ätherauszüge getrennt verarbeitet.

Extrakt I: In 1 cm Schichtdicke gemessen $E = 0.692$, entsprechend einer Konzentration von 1.02 mg%. In 50 ccm Extrakt sind demnach 0.51 mg enthalten.

Extrakt II: Keine Trübung.

Die Gesamtausbeute beträgt also 0.51 mg, entsprechend 102%.

4) 200 ccm Normalharn, mit 0.2 mg Sontochin versetzt, zweimal ausgeschüttelt, Ätherauszüge gemeinsam verarbeitet. In 1 cm Schichtdicke wurde abgelesen $E = 0.244$, entsprechend ~~xx~~ 0.41 mg%. In 50 ccm Extrakt sind also 0.205 mg enthalten, entsprechend einer Ausbeute von 103%.

Abgesehen vom ersten Versuch mit der verhältnismäßig großen Menge von 5.0 mg Sontochin lag in allen Fällen die Ausbeute höher als 100%. Dieses Ergebnis ist wohl so zu erklären, daß in den normalen Harnen in geringer Menge Stoffe enthalten sind, die zwar bei direkter Verarbeitung keine Trübung liefern, aber bei Gegenwart von Sontochin die Reaktion verstärken, so daß die gefundenen Werte zu hoch sind. Es ist aber bemerkenswert, daß selbst in dem Versuch mit dem geringsten Zusatz von Sontochin (0.2 mg) das Ergebnis keine untragbare Verfälschung aufweist. Man darf aber wohl 0.2 mg Sontochin in 200 ccm Harn (0.1 mg%) als die untere Grenze ansehen, bei der die Bestimmung noch zuverlässige Werte liefert.

Tabelle für die Sonotechin-Bestimmung.

Konzentration in mg%.

B	d = 2.0 cm	d = 1.0 cm	d = 0.5 cm
0.100		0.30	
0.110		0.31	
0.120		0.31	
0.130		0.32	
0.140		0.32	
0.150		0.33	
0.160		0.34	
0.170		0.35	
0.180		0.35	
0.190		0.36	
0.200	0.25	0.37	
0.210	0.25	0.38	
0.220	0.26	0.39	
0.230	0.26	0.40	
0.240	0.27	0.41	
0.250	0.27	0.42	
0.260	0.28	0.43	
0.270	0.28	0.44	
0.280	0.29	0.46	
0.290	0.30	0.47	
0.300	0.30	0.48	
0.310	0.31	0.49	
0.320	0.31	0.51	
0.330	0.32	0.52	
0.340	0.32	0.54	
0.350	0.33	0.55	0.98
0.360	0.34	0.57	1.02
0.370	0.34	0.58	1.04
0.380	0.35	0.59	1.07
0.390	0.36	0.61	1.10
0.400	0.36	0.62	1.13
0.410	0.37	0.64	1.15
0.420	0.38	0.65	1.18
0.430	0.38	0.66	1.21
0.440	0.39	0.68	1.24
0.450	0.39	0.69	1.26
0.460		0.70	1.29
0.470		0.72	1.32
0.480		0.73	1.35
0.490		0.74	1.38
0.500		0.76	1.41
0.510		0.77	1.44
0.520		0.79	1.46
0.530		0.80	1.49
0.540		0.82	1.52
0.550		0.83	1.55
0.560		0.84	1.58
0.570		0.86	1.61
0.580		0.87	1.64
0.590		0.88	1.67
0.600			

Tabelle für Sentochin-Bestimmung (Forts.).

Konzentration in mg%

<u>E</u>	<u>d = 1.0 cm</u>	<u>d = 0.5 cm</u>
0.600	0.90	1.70
0.610	0.91	1.74
0.620	0.92	1.77
0.630	0.93	1.81
0.640	0.95	1.85
0.650	0.96	1.89
0.660	0.98	1.94
0.670	0.99	1.98
0.680	1.00	2.03
0.690	1.02	2.07
0.700	1.03	2.12
0.710	1.05	2.17
0.720	1.06	2.22
0.730	1.08	2.27
0.740	1.09	2.31
0.750	1.11	2.37
0.760	1.12	2.42
0.770	1.13	2.47
0.780	1.15	2.53
0.790	1.16	2.58
0.800	1.18	2.63
0.810	1.19	2.68
0.820	1.21	2.72
0.830	1.22	2.75
0.840	1.23	2.78
0.850	1.25	
0.860	1.26	
0.870	1.27	
0.880	1.29	
0.890	1.30	
0.900	1.32	
0.910	1.33	
0.920	1.35	
0.930	1.36	
0.940	1.37	
0.950	1.39	
0.960	1.40	
0.970	1.41	
0.980	1.43	
0.990	1.44	
1.000	1.45	
1.010	1.47	
1.020	1.49	
1.030	1.50	

In der Tabelle fehlen die Werte für kleine Extinktionen (0.100 - 0.190) in 2.0 cm Schichtdicke, weil diese nach den Versuchen mit reinen Lösungen zu unsicher sind. Infolgedessen kommt man praktisch mit zwei Schichtdicken (0.5 und 2.0 cm) aus. - 187 -

The Serological Diagnosis of Spotted Typhus Under Condition
of Military Sanitation
by Dr. Hermann Eyer and Dr. Waldemar Brix.¹

Up to the present there has always been an urgent desire to assure the diagnosis of spotted typhus as soon as possible. This want has led to several researches of which none up to the present has been satisfactory.

The leading thought of all these researches has been the sensible use of the already known so-called "quick agglutination test" on the preparation slide, a method that has already been mentioned in previous publications.

Already in 1910 Bass and Watkins have published a method to be practiced at the bedside. The authors have mixed on a preparation slide a small amount of the patient's blood in question with a suspension of typhus- and para-typhus bacilli. After ten minutes already they could make their conclusions in case of agglutination. In ignorance of the researches of Bass and Watkins the same method has been discovered and recommended by Lewis twenty years later. Almost at the same time the American veterinary surgeons Bunyea, Hall and Dorset have applied to this method for the diagnosis of poultry diseases. The same technique has been practiced in 1938 by Castañeda and Silva for the diagnosis of spotted typhus. In 1940 also Brumpf, Eyer and Grützner as well as Kudicke and Steuer published successful experiments of this kind, and not before long Hallmann, Tietz and Carlé showed further modifications of this test.

Whilst former scientists have used this method entirely as a quick agglutination test neglecting any qualitative point of view, Kudicke and Steuer tried to develop the method in this respect.

Eyer and Grützner have not given any attention to the quantitative part and have studied this test only from the qualitative standpoint. It was necessary to confront this quantitative test with a rather simple and handy qualitative test that could probably give an instructive result without further preliminary knowledge or special instruments.

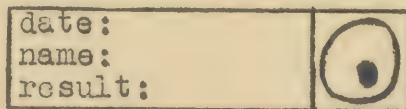
In the following we want to give a short report of the test that has been used during the season of spotted typhus that has just passed.

¹Der Deutsche Militärarzt 8:193-194, 1943

Beforehand we want to make clear that this new test deals only with the question whether from the serological standpoint spotted typhus can be diagnosed or not. Although for those who have some experience it might be easy to reckon at the height of the agglutinating titre the exact method by laboratory should not be neglected, unless of course several serological qualitative tests are negative. In any case, the technique mentioned below has the enormous privilege to enable us to take precautionary measures as soon as spotted typhus is suspected and to prevent further mischief.

We do not pretend that this "spotted-typhus foil test" as we call it is something new; only our application of the method has been unknown so far.

Instead of using the preparation slides of glass we took paper foils that have been used already by Brumpf for agglutination of bacteria and later on by Wagner to test blood-groups. It soon turned out that the transparent foils made of artificial stuff as they are used now-a-days for various purposes were more suitable to judge the agglutination than the so-called structureless papers. Formerly when preparation slides of glass were in use one took conserved, liquid and partly also coloured emulsions. But as the carrying about of such fluid reagents has turned out to be most inconvenient we have put the reagent ready to use on the test foil. One has only to make it swell by some drops of water and then to mix it with a small amount of the blood in question. The picture below shows our test foil in a scale of 3:5



If the titre of agglutination is within 1:640 and more you see the definite result at once; if the titre is within 1:160 and below you cannot judge it but a few minutes later.

The test itself is done in the following way:

Mix some drops of ordinary water by means of a little glass stick or a match with the reagents of the test foil (blue and white point) and make it dissolve by stirring it. Then mix thoroughly some drops of the patient's blood which you can take as usually out of his finger-tip with the blue coloured emulsion of bacteria. The grey-red coloured mixture of blood and bacteria has to be moved to and fro until in case of positive result after a short time (latest in 3 minutes) little blue coloured grains

are to be seen in the liquid. They quickly increase in size and show the tendency to roll to the edge of the mixture. Meanwhile the grey-red colour of the mixture turns into a pure red.

In case of a strong positive blood-test the grains are bigger and the colour is pure red.

In case of a medium titre the grains are smaller and the whole mixture is more of a grey-red colour.

In case of a negative result neither the colour nor the quality of the mixture changes its character.

The emmetropic can read the result microscopally, otherwise one ought to take a magnifying glass with enlargement of 1:6 or 1:8. You can judge the result distinctly even after the mixture has dried up, you may keep the foils for a long time, you only need protect them against insects.

As this method has been known for more than 30 years and has always been used successfully we need not publish our various experiments.

Only the new and most handy form of this foil test seems to us an addition especially to the sanitary officers working under the condition of war.

Abschrift

Der Deutsche Militärarzt, 1942 Nr. 6 Seite 399

Fleckfieber - Schnellreaktion

mit Trockendiagnostikum "Krakau".

Von Dr. Tietz, Oberstabsarzt, Armeehygieniker, Und Dr.phil. Carle

Die Bedeutung der serologischen Bestätigung der klinischen Fleckfieber-diagnose und der serologischen Klärung zweifelhafter Fälle hat es notwendig gemacht, unter Feldverhältnissen dem Kliniker selbst eine brauchbare Reaktion an die Hand zu geben, denn es ist nicht tragbar, dass sich bei den liegeverhältnissen im Osten während der Schne- und Schlampperioden die Einsendezeit des Untersuchungsmaterials über Tage erstreckt. Die Seuchenabwehrmaßnahmen erfordern eine rasche Klärung der Diagnose.

Die Fleckfieber- Schnellreaktion mit dem Trockendiagnosticum - "Krakau" ist eine Abwandlung der Weil-Felix-Reaktion. Die Reagenzien und die Ausführung der Reaktion sind auf die Möglichkeiten im Feldlazarett, ja sogar bei der Sanitätskompanie, abgestellt. Die Objektträgermethode - wie sie auch zur Blutgruppenbestimmung angewandt wird - ist die Methode der Wahl.

Von entscheidender Bedeutung ist die Frage der Bakterien - emulsion. Es ist unter Feldverhältnissen nicht möglich, dass die Untersuchungsstellen die Lazarette mit den notwendigen Bakterienemulsionen beliefern. Die Lazarette müssen die Aufschwemmungen selbst herstellen können. Dies ist allein mit dem Fleckfieber - Trockendiagnosticum Proteus O X 19 vom Institut für Fleckfieber- und Virusforschung Krakau möglich. Die Bakterienemulsion wird zur Verhinderung der Blutgerinnung und damit verbundener Vortäuschung falscher Ergebnisse mit Natriumcitrat- Kochsalzlösung oder mit Tutofusin angesetzt. Die Bereitung der Bakterienemulsion ist demnach in jeder Sanitätseinrichtung möglich.

Ansetzen der Bakterienemulsion. Der Inhalt der Ampulle Trockendiagnosticums wird in 2 ccm Natriumcitrat - Kochsalzlösung oder Tutofusin mit Natriumcitratzusatz die Lösung muss vorher nochmals durch Aufkochen sterilisiert werden und abkühlen - durch kräftiges Schütteln emulsiert. Die Aufschwemmung einer Ampulle reicht für 20 Reaktionen und ist bei zweckentsprechender Aufbewahrung gut eine Woche haltbar.

Durchführung der Reaktion. Bluttropfen aus dem Ohrläppchen - wie beim "Dicken Tropfen" - entnehmen und auf einen Objektträger tupfen. Einen Tropfen Bakterienemulsion mittels einer Tropfpipette neben den Bluttropfen setzen. Mit der Schmalseite eines zweiten Objektträgers beide Tropfen gut durchmischen. Objektträger bewegen und Agglutination beobachten. Die Reaktion sieht ähnlich aus wie bei der Blutgruppen-bestimmung. Bei positiver Reaktion verklumpen die Bakterien und drängen die roten Blutkörperchen zusammen. Tritte eine Veränderung des homogenen Bluttropfens innerhalb 3 Min. nicht auf, so ist die Reaktion als negativ zu bewerten. Bei sofort einsetzender Agglutination liegt der Titer bei 1: 3200 und darüber, bei Reaktionszeiten bis 1 Min. bei 1:1600, bis 2 Min. bei 1: 800, bis 3 Min. bei 1: 400. Es ist zweckmäßig, positive und negative Kontrollen mit anzusetzen.

Diese Reaktion ist nach langen Versuchsreihen so eingesetzt, dass sie von vornherein die unspezifischen Reaktionen weitestgehend ausschaltet, wie sie bei Hepatitis

epidemica, Typhus, Paratyphus und Enteritis, sowie bei Brucellosen in dem Schrifttum beschrieben sind. Bei den Untersuchungen in unserem Bereich werden in einem hohen Vonhundertsatz auch bei Wolhynischem Fieber und Hepatitis epidemica unspezifische Proteus O X 19-Agglutinationen beobachtet, die besonders störend für die serologische Fleck - fieberdiagnose sind.

Die Reaktion versichtet auf die niedrigen Titer 1: 200 und zeigt je nach der Stärke des Titers grob- bis feinschollige Agglutinationen, die je nach dem Zeitpunkt ihres Auftretens als Anhalt für den Agglutinationstiter gewertet werden können.

Diese Fleckfieberreaktion ist an einem grossen Krankengut auch verschiedener Volksgruppenzugehörigkeit geprüft und wird zur Zeit bei den Lazaretten als Probeagglutination ausgeführt. Sie gewinnt deswegen noch besondere Bedeutung, weil sie täglich am Krankenbett ausgeführt werden kann und so der Beginn der seropositiven Phase leicht zu erfassen ist, der um den 5. Krankheitstag auftritt und im Verlauf der Krankheit rasch ansteigt. Bei positivem Ausfall wird grundsätzlich noch zur WEIL-FELIX-Reaktion zur Feststellung des Titers an die Untersuchungsstellen eingeschickt.

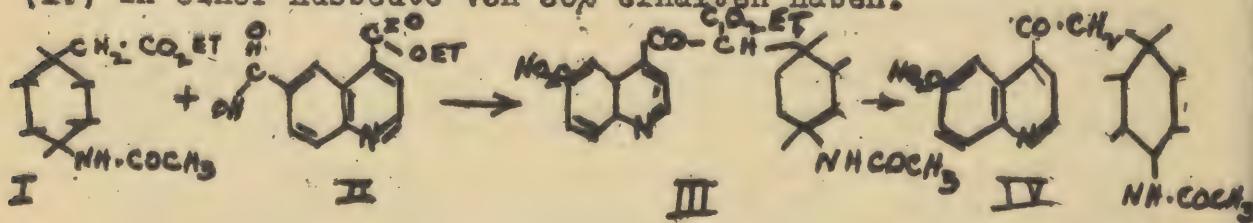
Darüber hinaus ermöglicht die Schnellreaktion die Durchuntersuchung von Bevölkerungsgruppen, bei denen die nachträgliche Feststellung einer Fleckfiebererkrankung notwendig ist. Besondere Bedeutung kommt hier aber der Bewertung der Titergrenze zu, da durch unspezifische Reaktion Wolhynisches Fieber häufig als Fleckfieber gestempelt wird und somit ein falsches Bild entstehen kann.

Nach Veröffentlichung des Vortrages wurden erst die Versüche von HALLMANN bekannt, der ähnliche Wege eingeschlagen hat. Die Veröffentlichung unserer Beobachtungen wird dennoch für wertvoll erachtet, weil die Verwendung des Trockendiagnosticums "Krakau" erst die Durchführung unter Feldverhältnissen, vor allem in den vorderen Sanitätseinrichtungen ermöglicht.

APPENDIX III

Arbeitsbericht DiplIng. G. Schmolke
abgeschlossen am 8. April 1941

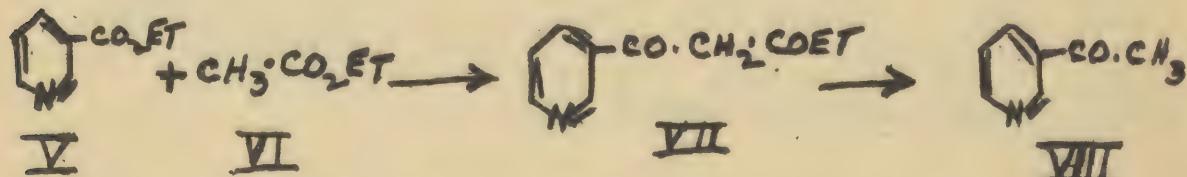
Am Schlus seiner Promotionsarbeit berichtet R. Bendix von dem Versuch, den *cis*-4-Acetylaminocyclohexylessigsäure-1-äthylester (I) mit Chininsäure-äthylester (II) nach der Methode von Claisen zu kondensieren. Bendix will nach längeren Versuchen den B-Ketonsäure-ester: 6-Methoxy-chinolyl-4-(4-acetylaminocyclohexyl essigsäure-1)-äthylester (III) sowie das dazugehörige Keton: 6-Methoxy-chinolyl-4-(4-acetylaminocyclohexyl-1-methyl)-keton (IV) in einer Ausbeute von 30% erhalten haben.



Der Versuch, *cis*-4-acetylaminocyclohexylessigsäure-äthylester mit 2-Methyl-cinchoninsäure-äthylester zu kondensieren, hatte zu keinem Ergebnis geführt. In Anknupfung an diese Arbeit wurde mir die Aufgabe gestellt, die Bedingungen der claisen'schen Esterkondensation aufzuklären.

Zunächst wurde zur Erlangung der Ausgangssubstanz die gesamte Arbeit Bendix nachgearbeitet. Im wesentlichen wurden die Angaben vor Bendix restlos bestätigt.

Um die Bedingungen der Claisen'schen Kondensation an einem etwa einfacheren Körper zu studieren, wurde zunächst Nikotinsäure-äthylester (V) mit Essigester (VI) kondensiert:



Der Nikotinsäure-äthylester würde nach der Methode von Camps wie folgt hergestellt: 40 g Nikotinsäure, 80 g abs. Alkohol, und 80 g konz. Schwefelsäure werden 3 Stunden auf dem Wasserbad gekocht, auf Eis gegossen, Soda alkalisch gemacht und ausgeäthert. Die Ätherische Lösung wird

getrocknte, der Ather verjagt. Zurück bleibt ein orange-farbenes Öl, welches bei 223° (Lit. 224° unkor.) unzersetzt destilliert. Ausbeute etwa 90%.

Kondensation: Aus 0,95 g Natrium wurde reines Alkoholat bereitet. Zu diesem wurden 10 g Nicotinsäure-äthylester, 5 g Essigester und 10 ccm trocknes Benzol hinzugefügt, und 21 Stunden auf dem Wasserbad gerührt. Aus der zunächst klaren Lösung scheidet sich mit der Zeit ein gelblicher Satz aus. Nach Beendigung der Kondensation wurde abgekühlt, mit KO 100 ccm Ather, 50 ccm Eiswasser und 10 ccm 25%iger Natronlauge versetzt und unumgesetztes Ausgangsprodukt ausgeäthert. Darauf wurde mit 10%iger Schwefelsäure Kongosäuer gemacht und extrahiert. Aus der trockenen ätherischen Lösung erhält man 3,2 g eines gold-gelben leicht-flüssigen stechend riechenden Ols. Dieses wurde mit 30 ccm 25%iger Schwefelsäure 2 Stunden lang verseift. Nach dem Abkühlen wurde Soda alkalisch gemacht und ausgeäthert. Man erhält ein gelbliches Öl, welches etwa bei -3° zu langen spiebigen Nadeln erstarrt.

Ein zweiter Ansatz wurde wie folgt bereitet: Aus 2,3 g (1/10 Mol) Natrium wurde Alkoholat bereitet, 15 g (1/10 Mol) Nikotinsäure-äthylester und 15 ccm Benzol hinzugefügt und 3 Stunden auf dem Wasserbad gerührt. Darauf wurden 17,6 g (2/10 Mol) Essigester zugegeben und 60 Stunden auf dem Wasserbad gerührt. Die Aufarbeitung erfolgte wie vorstehend.

Ausbeute: 4 g Keton (VIII) = 27% d.Th.

Phenylhydrazon (aus verdünntem Alkohol): F = 136° (Lit. 137°)
p-Nitrophenylhydrazon (aus verdünntem Alkohol) gold-gelbe verfilzte Nadeln. F = $233-34^\circ$ Zers.

Semicarbazone (aus Alkohol u. Ather) weiße Nadeln.
F = 221° Zers.

Das B-Acetylpyridin (VIII) wurde von Engler und Kiby durch trockene Destillation von nikotinsaurem Calcium mit Calciumacetat erhalten. Schlechter ist die Ausbeute bei der Destillation von saurem chinolinsaurem Calcium mit Calciumacetat.

Der Versuch, cis oder trans -p-Acetylamino-cyclohexylsuccinsäure-äthylester mit Nikotinsäure-äthylester zu kondensieren, führt trotz wiederholter Abänderung der Versuchsbedingungen zu keinem Erfolg.

Es wurden um die Reaktionsbedingungen der Claisenschen Kondensation aufzuklären, systematische Kondensationsversuche vorgenommen (Acetessigester, Benzoylessigester usw.). Bei dem Versuch p-Acetamino-benzoësäure-äthylester und Essigester mit Natriummetall zu kondensieren wurde festgestellt, daß das Natrium an die Stelle des Wasserstoffs in der Acetamino-gruppe tritt, eine Erscheinung, die von Acetanilid bekannt

ist. Diese Reaktionsfähigkeit des Wasserstoffe in der Acetaminogruppe muß auch für das frühere Miblinger aller Kondensationsversuche mit p-Acetylarnino-cyclohexyl-säure-äthylester verantwortlich gemacht werden.

Um diese Reaktionsfähigkeit des Iminowasserstoffs zu eliminieren wurden in den folgenden Versuchen basischere Gruppen als die Acetylgruppe eingeführt, oder ein zweiter Substituent eingeführt. So wurde z.B. p-Methyl-acetylarnino-benzoësäureäthylester dargestellt und mit Essigester kondensiert.

Methyl-acetylarnino-benzoësäureäthylester.

41,4 g p-Acetylarnino-benzoësäure-äthylester, 160 ccm Toluol und 4,6 g feiner Natriumdraht im Paraffinbad auf 110-115° erwärmt. (Die Badtemperatur darf nicht höher steigen, da sonst die Aminogruppe angegriffen wird.) Wenn alles Natrium in Lösung gegangen ist, läßt man die Temperatur auf 80-90° zurückgehen, und gibt einen Überschub (14 g) von Dimethylsulfat zu. Da ausgeschiedene zähe gelbe Natriumsalz des p-Acetylarnino-benzoësäure-äthylesters geht dabei in Lösung und nach einiger Zeit scheidet sich Na_2SO_4 aus. Nach Beendigung der Methylierung wird abgekühlt, mit Wasser versetzt und einige Zeit zur Zersetzung etwa noch vorhandenen Dimethylsulfats gerührt. Der p-Methylacetyl-arnino-benzoësäure-äthylester wird aus schwach alkalischer Lösung extrahiert, getrocknet, das Lösungsmittel verjagt. Der rohe Ester blieb flüssig; er wurde der Vakuumdestillation unterworfen. Kp_3 194-197°. Bei der Destillation wurde der Kühler mit Dampf geheizt, da sonst der Ester bereits im Kühler fest wurde. Das in der Vorlage auskristallisierte Destillationsprodukt ist noch mit einem goldgelben Öl behaftet. Man preßt es deshalb aus einem Tonteller ab und kristallisiert es 2-3 mal aus reinem Benzin um. Man erhält schließlich den Ester in dünnen schimmernden rein weißen Blättchen. $F = 60,5^\circ$. Ausbeute 69% Reinprodukt.

Analyse: E 9,402 mg T 20° p 737 mm 0,548 ccm N_2
N gef. 6,58% ber. 6,34%

Kondensation von p-Methyl-acetylarnino-benzoësäure-äthylester mit Essigester.

Zu 5,52 g (1/40 Mol) Methyl-acetylarnino-benzoësäure-äthylester in 5 ccm Benzol werden 0,57 g (2,5/40 Mol) Natrium gegeben, und die Reaktion durch Zugabe von 3 Topfen absolutem Alkohol in Gang gesetzt. Reaktionstemperatur 88°. 23 g (1/4 Mol) Essigester wurden ganz langsam zugetropft. Nach 24 Stunden haben sich am Rande gerade bemerkbare Partikelchen einer voluminösen, schwach gelb gefärbten Masse abgeschieden. Nach weiteren 24 Stunden hatte sich eine beträchtliche Menge des rotbraunen Natriumsalzes

abgeschieden. Die Natriumstückchen waren stark verkrustet. Nach 4 Tagen wurde die Reaktion abgebrochen, unumgesetztes Natrium, und unumgesetzter Ausgangsester entfernt, kongoauer gemacht und ausgeäthert. Der rotbraune ölige Biletonsaureester wurde sogleich mit 17 %iger Salzsäure verseift. Es wurde mit Soda abgestumpft und mit Natronlauge gegen Hiazol neutralisiert. Aus der anfangs milchigen Trübung kristallisierten bald kleine schillernde Blättchen aus. Diese wurde abfiltriert, aus verdünntem Alkohol 1:4 und ein zweites Mal aus Wasser umkristallisiert. Ausbeute 0,4 g Keton = 0,8 % d.Th. F = 101,5°.

Das erhaltene Produkt gibt mit p-Phenylhydrazine eine rotbrune bis rote Fällung (Keton). Mit Nitrit entsteht ein gelbes Nitrosamin (sekundäres Amin) mit diazotiertem p-Nitranilin fällt ein kanariengelber Farbstoff (o-Stellung der Aminogruppe frei). Die Substanz ist offenbar Monomethylaminoacetophenon.

Klingel will dieses aus Acetophenon und Methyljodid in Bombenrohr erhalten haben. Später stellte es auch Staudinger auf dieselbe Weise, sowie durch Methylierung von p-Amino-acetophenon her. Beide geben einen Schmelzpunkt von 58-59° an. Es konnte aber in unserem Institut nachgewiesen werden, daß es sich bei diesem Produkt um ein Gemisch von Mono- und Dimethylaminoacetophenon handelt. Bei obiger Esterkondensation kann nur das Monomethyl-Product entstehen. Dieses ist restlos identisch mit dem durch Methylierung von p-Amino-acetophenon und Reinigung über das Nitrosamin erhaltene Monomethyl-amino-acetophenon. Der Mischschmelzpunkt ergab keine Depression.

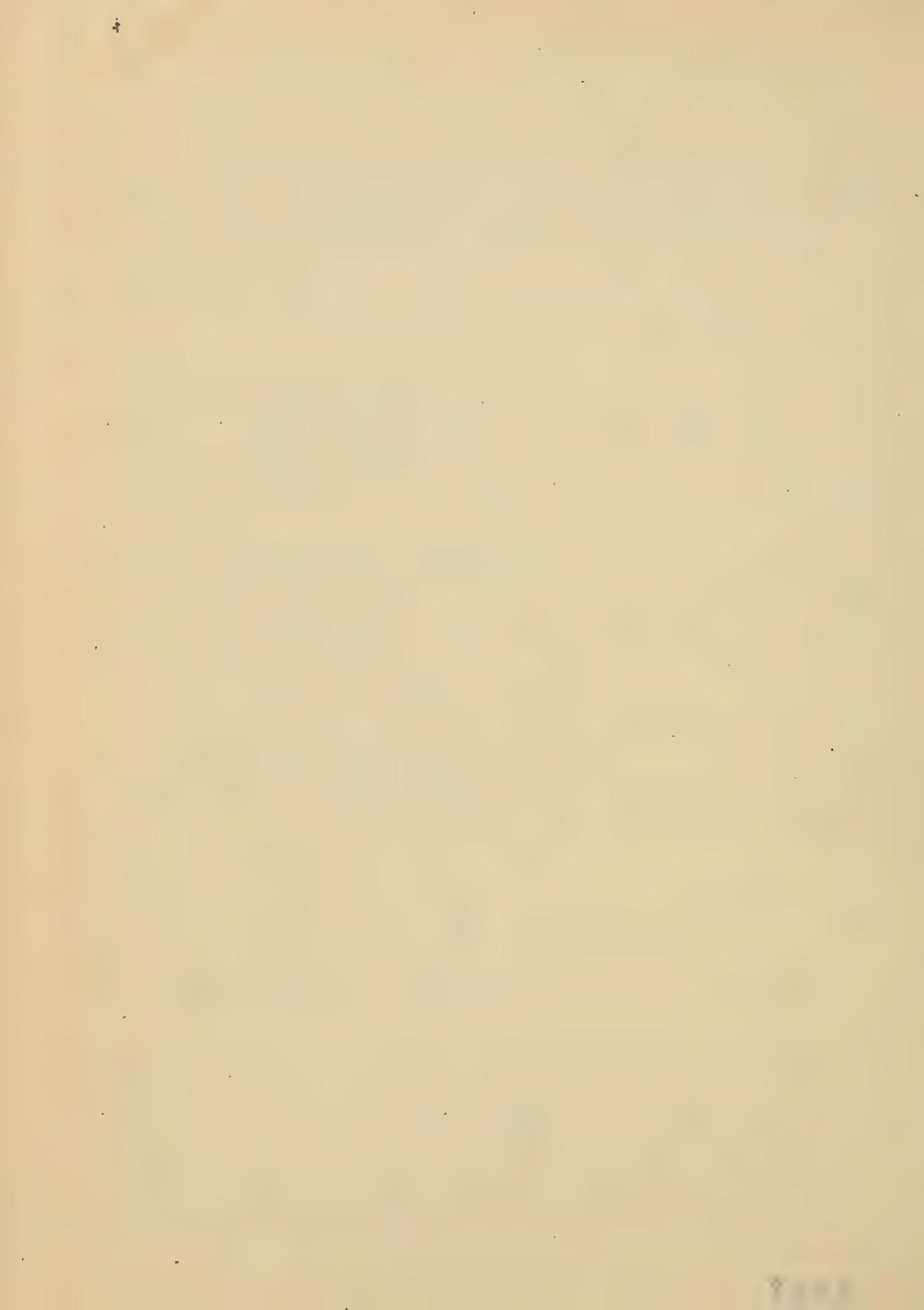
Analysen:



Berechnete:

Gefunden:

C	72,5	72,25
H	7,38	7,28
N	9,45	9,63





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